



## CLINICAL PROTOCOL

### A PHASE 3 RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED, MULTICENTER STUDY OF THE LONG-TERM SAFETY AND EFFICACY OF SUBCUTANEOUS ADMINISTRATION OF TANEZUMAB IN SUBJECTS WITH OSTEOARTHRITIS OF THE HIP OR KNEE

<b>Compound:</b>	PF-04383119
<b>Compound Name:</b>	Tanezumab
<b>United States (US) Investigational New Drug (IND) Number:</b>	BB-IND 11,680
<b>European Clinical Trial Database (EudraCT) Number:</b>	2012-003721-22
<b>Protocol Number:</b>	A4091058
<b>Phase:</b>	3

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**Document History**

Document	Version Date	Summary of Changes and Rationale
Amendment 2	15 May 2016	<p>Inclusion criterion #4 and associated text throughout the protocol has been updated to expand the number of pre-study, non-steroidal anti-inflammatory drug (NSAID) osteoarthritis pain treatment regimens that are considered to be qualifying. The following pre-study NSAID treatment regimens are now considered to be qualifying for prospective study subjects:</p> <p>Ibuprofen 1200 – 3200 mg/day</p> <p>Loxoprofen 120 – 180 mg/day</p> <p>Meloxicam 5 - 15 mg/day</p> <p>Nabumetone 1000 – 2000 mg/day</p> <p>Aceclofenac 200 mg/day</p> <p>Sulindac 200 – 400 mg/day</p> <p>Ketoprofen 200 mg/day</p> <p>To account for formulations of naproxen that include the sodium salt of naproxen, the lowest qualifying dose of naproxen is set at 440 mg/day.</p> <p>Exclusion criterion #21 has been updated to provide additional clarity regarding exclusion of subjects who have a history of heart block.</p> <p>Randomization criterion #9 and associated text in protocol Section 6.1.1 (Screening procedures) has been updated to provide a provision for re-selection of an index joint if the initially selected index joint does not have a qualifying Kellgren-Lawrence grade.</p> <p>Administrative updates in the Protocol Summary, Section 3, Section 5.8.2, Section 6.1.4 and 7.4.4 to:</p> <ul style="list-style-type: none"> <li>• Provide flexibility in the length of the Initial Pain Assessment Period (minimum of 3 days).</li> <li>• Provide clarification that the cost of standard</li> </ul>

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		<p>of care medication that subjects can receive 16 weeks after the last dose of subcutaneous study medication will be reimbursed by the sponsor if allowed per local regulation.</p> <ul style="list-style-type: none"> <li>• Provide clarification of the intended follow-up for subjects with severe and persistent joint pain.</li> </ul>
Amendment 1	10 July 2015	<p>Changes made in response to United States Food and Drug Administration Advice/Information Request (30 June 2015):</p> <ul style="list-style-type: none"> <li>• Inclusion criterion pertaining to inclusion of subject population with a prior history of failure, intolerance or unwillingness to take approved standard of care therapies for osteoarthritis pain has been added (Inclusion # 4).</li> <li>• Minor revisions in Protocol Summary, and protocol Sections 1.2.5, 3 have been updated to harmonize pre-study NSAID regimen text with updates in exclusion criterion 4 (noted above).</li> <li>• Protocol Sections 6.1 and 6.1.1 have been updated to reflect the required level of evidence to establish that subjects meet the updated inclusion criterion pertaining to inclusion of a subject population with a prior history of failure, intolerance or unwillingness to take approved standard of care therapies for osteoarthritis pain.</li> <li>• Required washout from rescue medication (acetaminophen / paracetamol) use before clinic visits has been decreased from 48 to 24 hours where applicable throughout the protocol.</li> </ul> <p>The Single Reference Safety Documents cited in Protocol Section 1.2.5 have been updated and relevant text in Section 5.6 has been harmonized with this update.</p>

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		<p>Definitions for completion of treatment and completion of study have been clarified in Protocol Section 3.</p> <p>Text pertaining to analysis of actigraphy data in Section 9.4.4.2 has been revised. Specific physical activity intensity thresholds have been removed from the protocol and will be available in the statistical analysis plan.</p> <p>Administrative changes (instructional text pertaining to archiving of completed PHQ-9 questionnaires in subject source documents and updates for consistency with Pfizer Protocol Template version 16 Feb 2015).</p>
Original protocol	01 April 2015	Not Applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

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function study in non-human primates, functional changes in the cardiovascular system controlled by the sympathetic nervous system were not observed.

Although evidence of clinically important effects on the sympathetic nervous system have not been identified in previously completed tanezumab studies, per agreement with the FDA, this and other clinical studies of tanezumab will incorporate additional safety measures to monitor for and manage subjects who may develop evidence of clinically important sympathetic nervous system dysfunction.

The primary objectives of this study are: 1) to characterize the long-term joint safety risks of tanezumab using a composite endpoint (includes adjudication outcomes of rapidly progressive osteoarthritis (type-1 and type-2), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture and 2) demonstrate the analgesic superiority of tanezumab relative to non-steroidal anti-inflammatory drugs (NSAIDs). Intravenous and subcutaneous (SC) administration of tanezumab at doses of 2.5 mg, 5 mg and 10 mg was shown to reduce pain and improve function in a dose-related manner in prior Phase 3 studies of osteoarthritis. No further study of the tanezumab 10 mg dose will be conducted in subjects with osteoarthritis as this dose did not provide any added efficacy benefit over the 5 mg dose. However, the 5 mg dose is expected to provide added efficacy benefit over the 2.5 mg dose. Tanezumab doses of 2.5 mg and 5 mg will be studied in this protocol.

The 56-week duration of the study precludes the use of a placebo comparator and as such, an active control has been included in the study design. To facilitate inclusion of an active control group that will serve as a benchmark for evaluation of the long-term safety and efficacy of tanezumab, subjects entering the current study must be receiving a stable dosing regimen of oral non-steroidal anti-inflammatory drugs (NSAID) therapy (naproxen, celecoxib, diclofenac, aceclofenac, loxoprofen, ibuprofen, meloxicam, nabumetone, sulindac or ketoprofen), be tolerating their NSAID regimen and be taking this medication regularly during the 30-day period prior to the Screening visit. Subjects randomized to receive NSAID in the current study will receive them at protocol specified doses [naproxen 500 mg twice a day (BID), diclofenac extended release (ER) 75 mg BID or celecoxib 100 mg BID]. The doses selected for the NSAID treatments being utilized in this study correspond to maximal or near maximal labeled doses for the treatment of osteoarthritis.

The study will include a number of assessments to permit further characterization of the pathophysiology of orthopedic events that may be observed during conduct of the study. These assessments are described in the main body of the protocol.

## **STUDY OBJECTIVES AND ENDPOINTS**

### **Primary Objectives:**

- Characterize the long-term risk of joint safety events in subjects with osteoarthritis of the knee or hip who receive tanezumab 2.5 mg or tanezumab 5 mg SC versus NSAID treatment (naproxen 500 mg BID, celecoxib 100 mg BID, or diclofenac ER

75 mg BID) over the course of 56-weeks of treatment using a composite endpoint (includes adjudication outcomes of rapidly progressive osteoarthritis type-1 or type-2, subchondral insufficiency fracture (SPONK), primary osteonecrosis, or pathological fracture).

- Demonstrate superior efficacy of tanezumab 2.5 mg and tanezumab 5 mg SC versus NSAID treatment (naproxen 500 mg BID, celecoxib 100 mg BID, or diclofenac ER 75 mg BID) at Week 16.

### **Secondary Objectives:**

- Characterize the long-term joint safety risk using a composite endpoint (includes adjudication outcomes of rapidly progressive osteoarthritis (type-2 only), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture).
- Characterize the long-term risk of the following individual adjudication outcomes occurring: rapidly progressive osteoarthritis (type-1 only), rapidly progressive osteoarthritis (type-2 only), rapidly progressive osteoarthritis (type-1 or type-2 combined), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, and pathological fracture.
- Characterize the long-term risk of all-cause total joint replacements (subjects who undergo total joint replacement plus subjects who have an adjudicated outcome of rapidly progressive osteoarthritis type-1 or type-2, subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture whether they undergo total joint replacement or not) occurring.
- Characterize joint space width changes in subjects with Kellgren-Lawrence Grade 2 or 3 osteoarthritis of the index knee or index hip.
- Demonstrate superior efficacy of tanezumab 5 mg and tanezumab 2.5 mg SC versus each separate NSAID treatment group (naproxen 500 mg BID, celecoxib 100 mg BID and diclofenac ER 75 mg BID) at Week 16.
- Demonstrate the efficacy of tanezumab 2.5 mg and tanezumab 5 mg SC versus NSAID (combined) treatment at all time points to Week 56.
- Evaluate the long-term safety of tanezumab 2.5 mg and tanezumab 5 mg SC.
- Explore relationships between adjudicated outcomes of rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture and variables that may be associated with these orthopedic risks.
- Characterize changes in physical activity level.

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### **Primary Endpoints:**

- Incidence of a predefined composite endpoint consisting of adjudication outcomes of rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture (primary composite endpoint).

The co-primary efficacy endpoints are:

- Change from Baseline to Week 16 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale.
- Change from Baseline to Week 16 in the WOMAC Physical Function subscale.
- Change from Baseline to Week 16 in the Patient's Global Assessment of Osteoarthritis.

*The Japanese Specific co-primary efficacy endpoints are:*

- *Change from Baseline to Week 16 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale.*
- *Change from Baseline to Week 16 in the WOMAC Physical Function subscale.*

### **Secondary Endpoints:**

#### **Bone and Joint Safety**

- Incidence of a predefined composite endpoint consisting of adjudication outcomes of rapidly progressive osteoarthritis (type-2 only), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture.
- Incidence of individual adjudication outcomes of rapidly progressive osteoarthritis (type-1 only), rapidly progressive osteoarthritis (type-2 only), rapidly progressive osteoarthritis (type-1 or type-2 combined), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, and pathological fracture.
- Incidence of all-cause total joint replacements (subjects who undergo total joint replacement plus subjects who have an adjudicated outcome of rapidly progressive osteoarthritis type-1 or type-2, subchondral insufficiency fracture (SPONK), primary osteonecrosis, or pathological fracture whether they undergo total joint replacement or not).

## Radiographic

- Change from Baseline to Week 56 and Week 80 in Medial or Lateral Minimum Joint Space Width of the index knee (for subjects with Kellgren-Lawrence Grade 2 or 3 medial or lateral osteoarthritis of the index knee).
- Change from Baseline to Week 56 and Week 80 in Minimum Joint Space Width of the index hip (for subjects with Kellgren-Lawrence Grade 2 or 3 osteoarthritis of the index hip).
- Incidence of subjects with progression of osteoarthritis in the index knee according to Bland and Altman method, at Week 56 and Week 80 (separately) (for subjects with Kellgren-Lawrence Grade 2 or 3 medial or lateral osteoarthritis of the index knee).
- Incidence of subjects with progression of osteoarthritis in the index hip according to Bland and Altman method, at Week 56 and Week 80 (separately) (for subjects with Kellgren-Lawrence Grade 2 or 3 osteoarthritis of the index hip).

## Efficacy

- WOMAC Pain subscale change from Baseline to Weeks 2, 4, 8, 24, 32, 40, 48, 56 and Week 64.
- WOMAC Physical Function subscale change from Baseline to Weeks 2, 4, 8, 24, 32, 40, 48, 56 and Week 64.
- Patient's Global Assessment of Osteoarthritis change from Baseline to Weeks 2, 4, 8, 16 (*Japan only*), 24, 32, 40, 48, 56 and Week 64.
- OMERACT-OARSI responder index at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- Treatment Response: Reduction in the WOMAC Pain subscale of  $\geq 30\%$ ,  $\geq 50\%$ ,  $\geq 70\%$  and  $\geq 90\%$  at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- Cumulative distribution of percent change from Baseline in the WOMAC Pain subscale score to Week 16, 24, and 56 (endpoint for summary only).
- Treatment Response: Reduction in the WOMAC Physical Function subscale of  $\geq 30\%$ ,  $\geq 50\%$ ,  $\geq 70\%$  and  $\geq 90\%$  at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- Cumulative distribution of percent change from Baseline in the WOMAC Physical Function subscale score to Week 16, 24, and 56 (endpoint for summary only).
- Treatment Response: Improvement of  $\geq 2$  points in Patient's Global Assessment of Osteoarthritis at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.

- Average pain score in the index joint change from Baseline to Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40, 48, 56 and Week 64.
- WOMAC Stiffness subscale change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- WOMAC Average change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- WOMAC Pain Subscale Item: Pain When Walking on a Flat Surface, change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- WOMAC Pain Subscale Item: Pain When Going Up or Down Stairs, change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI:OA) impairment scores change from Baseline to Weeks 16, 24, 56 and 64.
- EuroQol 5 Dimension (EQ-5D-5L™) dimensions and overall health utility score at Baseline and Weeks 8, 16, 24, 40, 56 and 64.
- Treatment Satisfaction Questionnaire Medicine v.II (TSQM v.II) satisfaction with effectiveness, side effects and convenience, and overall satisfaction at Weeks 16 and 56.
- Patient Reported Treatment Impact Assessment-Modified (mPRTI) at Weeks 16 and 56.
- Incidence and Time to discontinuation due to Lack of Efficacy.
- Usage of rescue medication (incidence and number of days of use) during Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- Usage of rescue medication (amount taken) during Weeks 2, 4, 8 and Week 16.
- Health Care Resource Utilization at Baseline, and Weeks 64, and 80.

### **Activity Level Monitoring**

- Lower Extremity Activity Scale: change from Baseline to Weeks 4, 8, 16, 24, 56 and Week 80 (all subjects).
- Change from Baseline to Weeks 16 and 56 in average daily minutes of physical activity (a subset of subjects).
- Change from Baseline to Weeks 16 and 56 in average daily physical activity counts (a subset of subjects).

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1. SC placebo (to match tanezumab) once every 8 weeks (a total of 7 administrations) plus NSAID administered orally (PO) (naproxen 500 mg BID PO, celecoxib 100 mg BID PO, or diclofenac ER 75 mg BID PO) through Week 56.
2. Tanezumab 2.5 mg SC once every 8 weeks (a total of 7 administrations) plus placebo BID PO (to match naproxen, celecoxib or diclofenac ER) through Week 56.
3. Tanezumab 5 mg SC once every 8 weeks (a total of 7 administrations) plus placebo BID PO (to match naproxen, celecoxib or diclofenac ER) through Week 56.

*Japan specific treatment groups are:*

1. *SC placebo (to match tanezumab) once every 8 weeks (a total of 7 administrations) plus celecoxib 100 mg BID administered orally (PO) through Week 56.*
2. *Tanezumab 2.5 mg SC once every 8 weeks (a total of 7 administrations) plus placebo BID PO to match celecoxib through Week 56.*
3. *Tanezumab 5 mg SC once every 8 weeks (a total of 7 administrations) plus placebo BID PO to match celecoxib through Week 56.*

The study is designed with a total duration of 80 weeks and will consist of three periods: Screening (up to a maximum of 37 days), Double-blind Treatment (56 weeks) and Safety Follow-up (24 weeks).

The Screening period (beginning 37 days prior to Randomization) includes a Washout period (lasting 2-30 days), if required, and an Initial Pain Assessment period (the 7 days prior to Baseline [Day 1]; minimum of 3 days). Prior to entering the study, subjects must be receiving a stable dosing regimen of oral NSAID therapy consisting of one of the NSAIDs presented in the following table, be tolerating their NSAID regimen and be taking this medication regularly (defined as an average of at least 5 days per week) during the 30-day period prior to the Screening visit.

**Qualifying Pre-study NSAID Treatment Regimens**

<b>NSAID</b>	<b>Qualifying Dose Range</b>
Naproxen	440 mg/day* to 1000 mg/day
Celecoxib	200 mg/day (either 100 mg BID or 200 mg QD)
Diclofenac	100 mg/day to 150 mg/day
Aceclofenac	200 mg/day
Loxoprofen	120 mg/day to 180 mg/day
Ibuprofen	1200 mg/day to 3200 mg/day
Meloxicam	5 mg/day to 15 mg/day
Nabumetone	1000 mg/day to 2000 mg/day
Sulindac	200 mg/day to 400 mg/day
Ketoprofen	200 mg/day

\*A minimum dose of 440 mg/day is applicable for naproxen formulations that include the sodium salt of naproxen otherwise the minimum qualifying dose of naproxen is 500 mg/day

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The Screening period will include collection of radiographs of the knees, hips, and shoulders (and other major joints exhibiting signs or symptoms suggestive of osteoarthritis) and magnetic resonance imaging (MRIs) of hips and knees. All radiographs will be evaluated by a Central Reader to determine the radiographic eligibility of subjects for the study.

The Double-blind Treatment period ends and the Safety Follow-Up Period begins at the Week 56 visit. Administration of SC investigational product (placebo, tanezumab 2.5 mg or tanezumab 5 mg) will occur during clinic visits at Baseline, Weeks 8, 16, 24, 32, 40 and 48. Subjects will self administer oral investigational product (NSAID or matching placebo) BID from the Baseline visit to Week 56 of the study. At Week 16 in the Double-blind Treatment period, the reduction in WOMAC Pain subscale score from Baseline will be calculated and only subjects meeting pre-defined response criteria may continue in the study. Subjects who do not meet pre-defined response criteria will be discontinued from the Double-blind Treatment period and enter the 24-week Early Termination Follow-up period. At Week 56, subjects will enter the Safety Follow-up period which lasts until Week 80.

Subjects who are discontinued from treatment prior to Week 56, either at their request or at the decision of the investigator, will be required to undergo 24 weeks of follow-up (referred to as Early Termination Follow-Up). The 24 weeks of follow-up will be obtained through 3 clinic visits and monthly phone calls to yield 24-weeks of post-treatment follow-up.

At Weeks 24, 56, and 80, all subjects will undergo repeat radiographs of each knee, hip and shoulder as well as any additional joint(s) that was imaged at Screening. At Week 24, confirmation of the continuing radiographic eligibility of the subject must be received from the Central Reader for subjects to continue receiving investigational product. Subjects with Kellgren-Lawrence Grade 3 or 4 osteoarthritis in any knee or hip joint, on the basis of the Central Reader's assessment of the screening radiographs, will have follow-up MRIs of each hip and knee obtained at Weeks 24, 56, and 80.

Subjects who have undergone or plan to undergo total joint replacement or other arthroplasty procedure during the study will be discontinued from investigational product. In addition, subjects who undergo total knee, hip or shoulder joint replacement surgery during the study (Treatment Period or Follow-up Period) will be followed for 24 weeks after the procedure as part of a separate protocol, provided the subject consents.

## STATISTICAL METHOD

A sample size of approximately 1000 subjects for each of the treatment groups of NSAID, tanezumab 2.5 mg and tanezumab 5 mg will be used in this study. This sample size allows for a high probability of observing subjects with any component of the composite endpoint where the event rate over this study is very small. If the event rate were 0.25%, then there would be a >90% probability of observing at least one subject with an event in any single treatment group. In addition, the sample size allows for good precision to estimate the incidence rate for each treatment group in order to estimate an upper bound for the true incidence rate.

## Primary Analysis

The incidence of subjects with any of the adjudication outcomes of the primary composite endpoint will be shown by number of subjects treated and subject years of exposure (treatment plus follow-up periods), for individual treatment groups and differences between tanezumab treatment groups and the NSAID treatment group. The risk ratio and risk difference with 95% confidence intervals will be calculated for the comparisons of each tanezumab treatment group versus the NSAID treatment group, as well as significance tests for each treatment comparison. The time to each event will be summarized, and (where there are sufficient numbers of subjects) Kaplan-Meier estimates of the time to event will be produced, together with an analysis of each tanezumab treatment group versus the NSAID treatment group using the log-rank test.

The primary safety and efficacy population will be the Intention-To-Treat (ITT) population, defined as all randomized subjects who received SC investigational product (either tanezumab or matching placebo). The primary efficacy analysis will use multiple imputation methods for missing data at Week 16. Details of the multiple imputation procedure are given below. All treatment comparisons will use the two-sided 5% significance level.

The co-primary efficacy endpoints will be analyzed using an Analysis of Covariance (ANCOVA) model, with model terms for Baseline score, Baseline Diary Average Pain, index joint (hip or knee), Kellgren-Lawrence grade, NSAID cohort (diclofenac, celecoxib or naproxen) and treatment group, and study site as a random effect. The assessment of significance for the tanezumab SC versus NSAID treatment contrasts of the primary efficacy parameters will use a step-down testing strategy within each of the co-primary efficacy endpoints. This order of significance testing is defined as first testing tanezumab 5 mg versus NSAID, and if statistically significant ( $p \leq 0.05$ ) to then test tanezumab 2.5 mg versus NSAID. Finally, the tanezumab treatment group is declared as superior to NSAID if the corresponding treatment contrast is significant over all three co-primary endpoints (*two co-primary efficacy endpoints in Japan*). This testing procedure will maintain the Type I error to 5% or less within each of the co-primary efficacy endpoints, and to less than 5% for all three co-primary efficacy endpoints (*two co-primary efficacy endpoints in Japan*).

The primary analysis of the co-primary endpoints will use multiple imputation for missing data, to account for uncertainty around the subject response. The basis for imputing missing values will be dependent on the reasons for missing data. For subjects with missing data due to discontinuation prior to Week 16 for lack of efficacy or for an adverse event or death, imputation will be based on sampling from a normal distribution using a mean value equal to the subject's baseline efficacy value and the standard deviation of the observed efficacy data at Week 16 (over all treatment groups). For subjects with missing data for any other reason, imputation will be based on sampling from a normal distribution using a mean value equal to the subject's last observed efficacy value and standard deviation of the observed efficacy data at Week 16 (over all treatment groups). Imputed values for the Patient's Global Assessment of Osteoarthritis will be rounded to integer values from 1 to 5 (*For Japan, Patient's Global Assessment of Osteoarthritis scores will not be imputed or used in the primary efficacy analysis*). Imputed values for the WOMAC Pain and Physical Function



**Table 1. Schedule of Activities**

The Schedule of Activities tables provide an overview of the protocol visits and procedures. Refer to **STUDY PROCEDURES** and **ASSESSMENTS** sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

**SCREENING SCHEDULE OF EVENTS**

Visit Identifier	Screening <sup>a</sup> (Day -37 to Day -1)		
	Screening Stage 1	Screening Stage 2	Initial Pain Assessment Period (IPAP)
	Day -37 to Day -7		Day -7 to Day -1
Informed Consent	X		
Numeric Pain Scale rating for bilateral shoulders, hips, knees and any other major joint that is imaged [Interactive Response Technology (IRT)]	X		
Primary Diagnosis/selection of index joint	X		
Demographics, General and Musculoskeletal Specific Medical History and Prior/Current medication Use <sup>b</sup>	X		
General Physical Examination	X		
Musculoskeletal Physical Examination <sup>c</sup>	X		
Weight/Height/BMI/Smoking Status/Female Hormonal Status/Alcohol Use	X		
Sitting Vital Signs (BP, HR)	X		
Orthostatic Blood Pressure (supine/standing)	X		
Electrocardiogram (ECG 12-lead)	X		
Neurologic Exam - Neuropathy Impairment Score (NIS) <sup>d</sup>	X		
WOMAC Pain, Physical Function and Stiffness Subscales (for index hip or knee) <sup>i</sup>	X		
Survey of Autonomic Symptoms (SAS) questionnaire <sup>l</sup>	X		
Subjects Trained on use of IRT System		X	
Subject Daily/Weekly Assessments (IRT) <sup>p</sup>			X
Washout of Prohibited Pain Medications	→		
Inclusion/Exclusion Criteria	X		
Female Subjects of Child-bearing Potential Instructed on Contraceptive Requirements for Study	X		
<b>IMAGING</b>			
Radiographs of each Hip, Knee and Shoulder	X		
Collect Local Radiography Report	X		
Magnetic Resonance Imaging (MRI) each hip and knee <sup>e</sup>			X
Dual-Energy X-ray Absorptiometry (DXA) per National Osteoporosis Foundation Guidelines <sup>e</sup>			X
<b>ACTIVITY LEVEL MONITORING</b>			
Actigraphy <sup>l</sup>			X
<b>LABORATORY</b>			
Hepatitis Screen (Hepatitis B & Hepatitis C); HIV test, Urine Toxicology screen	X		
HbA1c	X		
Serum FSH Test <sup>g</sup>	X		
Serum Pregnancy Test	X		
Hematology	X		
Blood Chemistry	X		

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Visit Identifier	Screening <sup>a</sup> (Day -37 to Day -1)		
	Screening Stage 1	Screening Stage 2	Initial Pain Assessment Period (IPAP)
Urinalysis	X		
<b>PRE-STUDY NSAID / RESCUE MEDICATION</b>			
Pre-study NSAID Dispensed/Regimen Stabilization <sup>h</sup>	X	At least 2 weeks prior to Baseline (Day 1) visit	
Oral Rescue Medication Dispensed	X		
Abbreviations: → = ongoing/continuous event; BMI = Body Mass Index; BP = Blood Pressure; DXA = Dual Energy X-ray Absorptiometry; ECG = electrocardiogram; FSH = Follicle Stimulating Hormone; HbA1c = Glycosylated Hemoglobin; HR = Heart Rate; HIV = Human Immunodeficiency Virus; IRT = Interactive Response Technology; MRI = Magnetic Resonance Imaging; NIS = Neuropathy Impairment Score; NSAID = Non-Steroidal Anti-Inflammatory Drug; SAS = Survey of Autonomic Symptoms; WOMAC = Western Ontario and McMaster University Osteoarthritis Index			

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**DOUBLE-BLIND TREATMENT AND SAFETY FOLLOW-UP PERIOD SCHEDULE OF EVENTS**

Visit Identifier	Double-Blind Treatment									Safety Follow-up		
	Baseline <sup>k</sup>	Week 2	Week 4	Week 8 <sup>k</sup>	Week 16 <sup>k</sup>	Week 24 <sup>k</sup>	Week 32 <sup>k</sup>	Week 40 <sup>k</sup>	Week 48 <sup>k</sup>	Week 56 End of Treatment	Week 64	Week 80 End of Study
	Day 1	Day 15	Day 29	Day 57	Day 113	Day 169	Day 225	Day 281	Day 337	Day 393	Day 449	Day 561
Visit Window		±3 days	±3 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
General Physical Examination										X		
Musculoskeletal Physical Examination <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Sitting Vital Signs (BP, HR)	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic Blood Pressure (supine/standing)	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG 12-lead)										X		X
Body Weight										X		
Survey of Autonomic Symptoms (SAS) questionnaire <sup>i</sup>						X				X		X
Neurologic Exam Neuropathy Impairment Score (NIS) <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria/ Subject Eligibility	X				X <sup>s</sup>	X <sup>s</sup>						
Randomization	X											
<b>IMAGING</b>												
Radiographs of each Hip, Knee and Shoulder						X				X		X
Collect Local Radiography Report						X				X		X
Magnetic Resonance Imaging (MRI) of each hip and knee <sup>q</sup>						X				X		X

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Visit Identifier	Double-Blind Treatment									Safety Follow-up		
	Baseline <sup>k</sup>	Week 2	Week 4	Week 8 <sup>k</sup>	Week 16 <sup>k</sup>	Week 24 <sup>k</sup>	Week 32 <sup>k</sup>	Week 40 <sup>k</sup>	Week 48 <sup>k</sup>	Week 56 End of Treatment	Week 64	Week 80 End of Study
	Day 1	Day 15	Day 29	Day 57	Day 113	Day 169	Day 225	Day 281	Day 337	Day 393	Day 449	Day 561
Visit Window		±3 days	±3 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
<b>ACTIVITY LEVEL MONITORING</b>												
Lower Extremity Activity Scale (LEAS)	X		X	X	X	X				X		X
Sites provide accelerometers to subjects <sup>f</sup>				X <sup>f</sup>					X <sup>f</sup>			
Actigraphy <sup>f</sup>					X <sup>f</sup>					X <sup>f</sup>		
Sites collect accelerometers from subjects <sup>f</sup>	X <sup>f</sup>				X <sup>f</sup>					X <sup>f</sup>		
<b>LABORATORY</b>												
Serum/Urine Pregnancy Test	X			X	X	X	X	X	X	X	X	
Hematology	X				X						X	
Blood Chemistry	X				X						X	
Serum 25-hydroxy vitamin D and parathyroid hormone	X										X	
Serum and Plasma Retention Samples	X				X					X	X	
Banked biospecimen (whole blood)	X											
<b>PHARMACOKINETIC, PHARMACODYNAMIC AND BIOMARKER SAMPLING</b>												
Plasma Pharmacokinetic Sample <sup>n</sup>	X			X	X		X		X	X	X	
Serum NGF (PD) Sample <sup>n</sup>	X			X					X	X	X	
Serum Anti-tanezumab Antibody <sup>n</sup>	X			X	X		X		X	X	X	X
Serum and Urine Biomarkers <sup>n</sup>	X			X	X		X <sup>o</sup>		X <sup>o</sup>	X <sup>o</sup>	X <sup>o</sup>	X <sup>o</sup>
Synovial Fluid Sample												Optional for subjects undergoing arthrocentesis; additional sampling may be needed <sup>l</sup>

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Visit Identifier	Double-Blind Treatment									Safety Follow-up		
	Baseline <sup>k</sup>	Week 2	Week 4	Week 8 <sup>k</sup>	Week 16 <sup>k</sup>	Week 24 <sup>k</sup>	Week 32 <sup>k</sup>	Week 40 <sup>k</sup>	Week 48 <sup>k</sup>	Week 56 End of Treatment	Week 64	Week 80 End of Study
	Day 1	Day 15	Day 29	Day 57	Day 113	Day 169	Day 225	Day 281	Day 337	Day 393	Day 449	Day 561
Visit Window		±3 days	±3 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
<b>SUBJECT DAILY / WEEKLY ASSESSMENTS (IRT)</b>												
Numeric Pain Scale rating	Daily Entries for Index Joint and Weekly For Non-index Joints						Weekly Entries for Index and Non-index Joints					
Rescue Medication Use	Daily Entries						Weekly Entries					
Concomitant NSAID Use	Weekly Entries											
<b>STUDY TREATMENTS / RESCUE MEDICATION / STANDARD OF CARE</b>												
Subcutaneous Investigational Product Administered	X			X	X	X	X	X	X			
Oral investigational product (NSAID or matching placebo) Dosing	X	Self administered by subjects BID →										
Oral investigational product (NSAID or matching placebo) Dispensed and/or Compliance Check	X	X	X	X	X	X	X	X	X	X		
Oral Rescue Medication Dispensed and/or Compliance Check <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X	
Assign Standard of Care Treatment as Needed <sup>m</sup>											X	
<b>SUBJECT REPORTED ASSESSMENTS (Completed at Study Visits)<sup>l</sup></b>												
WOMAC Pain, Physical Function and Stiffness Subscales (for index hip or knee)	X	X	X	X	X	X	X	X	X	X	X	
Patient's Global Assessment of Osteoarthritis	X	X	X	X	X	X	X	X	X	X	X	
WPAI:OA	X				X	X				X	X	
EQ-5D-5L	X			X	X	X			X	X	X	
TSQM (v.II)					X					X		
mPRTI					X					X		

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Visit Identifier	Double-Blind Treatment									Safety Follow-up		
	Baseline <sup>k</sup>	Week 2	Week 4	Week 8 <sup>k</sup>	Week 16 <sup>k</sup>	Week 24 <sup>k</sup>	Week 32 <sup>k</sup>	Week 40 <sup>k</sup>	Week 48 <sup>k</sup>	Week 56 End of Treatment	Week 64	Week 80 End of Study
	Day 1	Day 15	Day 29	Day 57	Day 113	Day 169	Day 225	Day 281	Day 337	Day 393	Day 449	Day 561
Visit Window		±3 days	±3 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
Health Care Resource Utilization Assessment	X										X	X
<b>OTHER ASSESSMENTS / PROCEDURES</b>												
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X
Review Compliance With Subject IRT Entry and Data Review <sup>p</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Female Subjects of Childbearing Potential Reminded of Contraceptive Requirements	X	X	X	X	X	X	X	X	X	X		
Telephone Contact With Subjects <sup>r</sup>										Phone contact with subject will be made at Weeks 12, 20, 28, 36, 44, 52, 60, 68, 72 and 76		
Abbreviations: → = ongoing/continuous event; BID = Twice daily; BP = Blood Pressure; ECG = electrocardiogram; HR = Heart Rate; HCRU = Health Care Resource Utilization; EQ-5D-5L = EuroQol 5 Dimension; IRT = Interactive Response Technology; LEAS = Lower Extremity Activity Scale; mPRTI = Patient Reported Treatment Impact assessment-modified; MRI = Magnetic Resonance Imaging; NGF = Nerve Growth Factor; NIS = Neuropathy Impairment Score; NSAID = Non-Steroidal Anti-Inflammatory Drug; PD = Pharmacodynamics; SAS = Survey of Autonomic Symptoms; TSQM (v.II) = Treatment Satisfaction Questionnaire Medicine version II; WOMAC = Western Ontario and McMaster University Osteoarthritis Index; WPAI:OA = Work Productivity and Activity Impairment Questionnaire: Osteoarthritis												

**Early Termination Schedule of Events<sup>j</sup>**

Visit Identifier	As soon as possible after determining subject will be discontinued from study	Early Termination Visit 1	Early Termination Telephone Contact 1 <sup>r</sup>	Early Termination Visit 2	Early Termination Telephone Contact 2 <sup>r</sup>	Early Termination Visit 3
		~8 Weeks after last SC dose	~12 Weeks after last SC dose	~16 Weeks after last SC dose	~20 Weeks after last SC dose	~24 Weeks after last SC dose
Radiographs of each Hip, Knee and Shoulder	X					X
Collect Local Radiography Report	X					X
Magnetic Resonance Imaging (MRI) of each hip and knee <sup>q</sup>	X					X
General Physical Examination		X				
Musculoskeletal Physical Examination <sup>c</sup>		X		X		X
Vital Signs (BP, HR)		X		X		X
Orthostatic Blood Pressure (supine/standing)		X		X		X
Body Weight		X				
Electrocardiogram (ECG 12-lead)		X				X
Survey of Autonomic Symptoms (SAS) questionnaire <sup>i</sup>		X				X
Neurologic Exam Neuropathy Impairment Score (NIS) <sup>d</sup>		X		X		X
Lower Extremity Activity Scale (LEAS)		X		X		X
Subject Weekly Assessments (IRT)	—————→					
Review Compliance With Subject IRT Entry and Data Reviewp		X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X
Female Subjects of Childbearing Potential Reminded of Contraceptive Requirements		X	X			

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Visit Identifier	As soon as possible after determining subject will be discontinued from study	Early Termination Visit 1	Early Termination Telephone Contact 1 <sup>r</sup>	Early Termination Visit 2	Early Termination Telephone Contact 2 <sup>r</sup>	Early Termination Visit 3	
		~8 Weeks after last SC dose	~12 Weeks after last SC dose	~16 Weeks after last SC dose	~20 Weeks after last SC dose	~24 Weeks after last SC dose	
<b>SUBJECT REPORTED ASSESSMENTS (Completed at Study Visits)<sup>l</sup></b>							
WOMAC Pain, Physical Function and Stiffness Subscales		X		X			
Patient's Global Assessment of Osteoarthritis		X		X			
WPAI:OA		X		X			
EQ-5D-5L		X		X			
TSQM (v.II)		X					
mPRTI		X					
Health Care Resource Utilization				X		X	
<b>RESCUE MEDICATION / STANDARD OF CARE</b>							
Concomitant Medication Review		X	X	X	X	X	
Oral Rescue Medication Dispensed <sup>l</sup>		X		X			
Oral Rescue Medication Return and Compliance Check		X		X			
Assign Standard of Care Treatment as Needed <sup>m</sup>				X			
<b>LABORATORY</b>							
Serum Pregnancy Test		X		X			
Hematology				X			
Blood Chemistry				X			
Serum and Plasma Retention Samples		X		X			
Serum Anti-tanezumab Antibody <sup>n</sup>		X		X		X	
Plasma Pharmacokinetic sample <sup>n</sup>		X		X			
Serum NGF (PD) sample <sup>n</sup>		X		X			
Serum and Urine Biomarkers <sup>n</sup>		X <sup>o</sup>		X <sup>o</sup>		X <sup>o</sup>	
Synovial Fluid Sample		Optional for subjects undergoing arthrocentesis; additional sampling may be needed <sup>l</sup>					
Serum 25-hydroxy vitamin D and parathyroid hormone				X			

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Visit Identifier	As soon as possible after determining subject will be discontinued from study	Early Termination Visit 1	Early Termination Telephone Contact 1 <sup>r</sup>	Early Termination Visit 2	Early Termination Telephone Contact 2 <sup>r</sup>	Early Termination Visit 3
		~8 Weeks after last SC dose	~12 Weeks after last SC dose	~16 Weeks after last SC dose	~20 Weeks after last SC dose	~24 Weeks after last SC dose
Abbreviations: → = ongoing/continuous event; BP = Blood Pressure; ECG = electrocardiogram; HR = Heart Rate; HCRU = Health Care Resource Utilization; EC = ethics committee; EQ-5D-5L = EuroQol 5 Dimension; IRT = Interactive Response Technology; LEAS = Lower Extremity Activity Scale; mPRTI = Patient Reported Treatment Impact assessment-modified; MRI = Magnetic Resonance Imaging; NGF = Nerve Growth Factor; NIS = Neuropathy Impairment Score; NSAID = Non-Steroidal Anti-Inflammatory Drug; PD = Pharmacodynamics; SAS = Survey of Autonomic Symptoms; TSQM (v.II) = Treatment Satisfaction Questionnaire Medicine version II; WPAI:OA = Work Productivity and Activity Impairment Questionnaire: Osteoarthritis						

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- a. The Screening period begins up to a maximum of 37 days prior to randomization and lasts a minimum of 14 or 21 days, allowing completion of the 2 or 3 week period of pre-randomization NSAID regimen stabilization (refer to [Section 6.1.1](#) for additional detail regarding NSAID regimen stabilization). Prior to entering the IPAP, subjects must washout from prohibited pain medications for at least 5 half-lives or 48 hrs (which ever is greater). During the IPAP, diary entries (joint pain and rescue medication use) must be provided for a minimum of 3 days in the 7 days immediately preceding randomization.
- b. At Screening, a comprehensive musculoskeletal medical history is obtained and will include current and past history of osteoarthritis, osteoporosis, osteopenia, other musculoskeletal syndromes, orthopedic surgeries (including arthroscopic procedures) ligament tear or rupture, gout and fracture. All treatments used to treat osteoarthritis and osteoarthritis pain.
- c. A musculoskeletal directed physical examination will be performed at each study visit; findings will be recorded on a case report form and findings considered clinically significant will be reported as adverse events. This physical examination is described in [Section 7.3.2](#).
- d. A neurological examination (NIS) will be performed by the Investigator (or designated physician) at each study visit and assessed for clinically significant changes from Baseline. Requirements for neurological consultation at which a full neurological examination is to be performed by a neurologist are detailed in [Section 7.3.13](#).
- e. Magnetic Resonance Images and Dual Energy X-ray Absorptiometry scans (if applicable, refer to [Section 7.3.11](#) and [Section 7.3.12](#)) should only be completed after the subject has been determined to be eligible from a radiographic perspective as per the Central Reader.
- f. Actigraphy will only be performed at selected sites. Actigraphy performed during the Screening period should only be completed after the subject has been determined to be eligible from a radiographic perspective as per the Central Reader. Actigraphy will also be performed at approximately Week 16 (between Weeks 14 and 16) and Week 56 (between Weeks 54 and 56), refer to [Section 7.3.9](#).
- g. FSH testing in female subjects as described in [Section 7.3.3.4](#).
- h. Pre-study NSAIDs will be dispensed in the Screening period and subjects will be required to maintain at least 70% (5 of 7 days per week) compliance during the final two or three weeks of the Screening period immediately prior to Baseline (Day 1) (refer to [Section 6.1.1](#) for additional detail regarding NSAID regimen stabilization).
- i. The WOMAC subscales, Patient's Global Assessment of Osteoarthritis, WPAI:OA, EQ-5D-5L and TSQM (v.II), mPRTI, Health Care Resource Utilization and Survey of Autonomic Symptoms questionnaires will be administered at site visits using IRT.
- j. Subjects discontinuing the study at their request or at the decision of the Investigator prior to Week 56 should be withdrawn from treatment and begin the 24-week Early Termination Follow-Up period described in [Section 6.4](#). Subjects who undergo total joint replacement will be followed for 24 weeks after the procedure as described in [Section 6.4.2](#).
- k. All study activities at dosing visits (Baseline [Day 1] and Weeks 8, 16, 24, 32, 40 and 48), including sample collection, are performed prior to dosing, unless otherwise noted.
- l. Rescue medication should be discontinued at least 24 hours prior to any on site study visit up to and including Week 64 (including during the Early Termination Follow-Up period). Subjects should return rescue medication bottles at each study visit for assessment of compliance.
- m. If needed, following completion of the visit at which final efficacy assessments are collected (Week 64 and/or 16 weeks after the last dose of investigational product administered), standard of care treatment (as described in [Section 5.8.2](#)) may be initiated, and usage recorded on the appropriate concomitant medication CRF.
- n. Samples for Anti-tanezumab Antibody, PK, NGF and biomarkers should be obtained pre-dose (if applicable to the visit). Biomarker samples should be collected at approximately the same time of the day at all scheduled time points and following a fasting period of at least 8 hours.
- o. Serum and urine biomarker sample collections at Weeks 32, 48, 56, 64 and 80 (or at early termination) will occur only for subjects that have activity level monitoring via accelerometry (N ~360).

- p. Subject Daily/Weekly Assessments (IRT) – Review of joint pain scores, rescue medication use and concomitant NSAID use entries (refer to [Section 7.1](#)). Compliance with IRT assessments is to be reviewed at each study visit, including Phone visits.
- q. Post-baseline MRIs will only be performed for subjects with Kellgren-Lawrence Grade 3 or 4 osteoarthritis in any knee or hip joint, on the basis of the Central Reader’s assessment of the Screening X-rays (refer to [Section 7.3.11](#)).
- r. To assess compliance with oral investigational product, concomitant medication use, conduct IRT entry review and compliance check, update adverse events, assess completion of actigraphy (Weeks 12 and 52 if applicable), verify follow-up radiographs and MRIs (if applicable) are scheduled (Weeks 20, 52 and 76), provide contraceptive requirement reminder as appropriate.
- s. At the Week 16 visit, subjects must have a 30% or greater reduction in WOMAC Pain subscale relative to Baseline in the index joint and a 15% or greater reduction in WOMAC Pain subscale from Baseline at either Week 2, 4 or 8 in order to continue investigational product. At Week 24, the continuing eligibility check will be based upon Central Reader review of radiographs (each hip, knee and shoulder) collected for the Week 24 visit.
- t. Synovial fluid sample collection is not a scheduled or required protocol procedure. Synovial fluid samples will only be collected for subjects who at the recommendation of the investigator, have arthrocentesis performed. Subjects will be asked to provide informed consent for analysis of the synovial fluid sample and potentially collection (if not already being collected at a scheduled timepoint) and analysis of additional blood samples for analysis of tanezumab pharmacokinetics, NGF and biomarkers (refer to [Sections 7.4.7, 7.5.1, 7.5.2, 7.5.3, 7.6.3](#)). Sample processing instructions are provided in the Laboratory Manual.

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## 1. INTRODUCTION

### 1.1. Mechanism of Action/Indication

Tanezumab (PF-04383119, formerly RN624) is an anti-nerve growth factor monoclonal antibody under development for the relief of signs and symptoms of osteoarthritis (OA).

### 1.2. Background and Rationale

#### 1.2.1. Role of Nerve Growth Factor in the Modulation of Pain

During mammalian development, nerve growth factor (NGF) is required for the survival and growth of several populations of neurons. In adults, the effect of NGF signaling shifts from the regulation of neuronal survival to the regulation of neuronal phenotype and function. The role of NGF in the adult mammal appears to principally be as a modulator of nociceptive neuronal activity. Thus, NGF plays an important role in modulation of the pain response.<sup>5,6</sup> Many studies employing a variety of antibodies to NGF or tropomyosin receptor kinase A (trkA)-IgG fusion protein have demonstrated that blocking NGF bioactivity normalizes pain sensitivity, particularly in states of allodynia and hypersensitivity, following a variety of insults such as Freund's adjuvant, carrageenan, or surgical incision.<sup>6,7</sup>

Both interleukin (IL)-1 $\beta$  and tumor necrosis factor alpha (TNF- $\alpha$ ) have been shown to induce synthesis of NGF. Inhibition of NGF in turn blocks the hyperalgesia experienced after administration of these cytokines.<sup>8,9</sup> Together these observations suggest that NGF may play a role in pain secondary to inflammation or injury.

#### 1.2.2. Description of Investigational Product

Tanezumab is a humanized immunoglobulin G Type 2 (IgG<sub>2</sub>) monoclonal antibody, derived from a murine precursor by grafting the murine complementarity determining regions onto a human antibody framework, followed by extensive site-directed mutagenesis using proprietary technology to improve binding affinity and specificity. A mutation was performed in the Fc portion of the antibody to decrease its ability to activate complement or to support antibody dependent cell-mediated cytotoxicity.<sup>10,11</sup>

Tanezumab is highly potent in sequestering NGF and preventing interaction with the trkA or p75 receptors. Tanezumab and/or the murine precursor have been shown to be an effective analgesic in nonclinical animal models of pathological pain including arthritis, cancer pain, and post-surgical pain models.<sup>12</sup>

#### 1.2.3. Overview of Clinical Studies

A total of 32 clinical studies involving over 11,000 patients have been conducted with tanezumab as of September 2014. Approximately 9,810 healthy volunteers or patients have been treated with tanezumab in non-cancer pain clinical studies. In patients treated with tanezumab monotherapy or tanezumab + NSAID in completed non-cancer pain studies, treatment experience with tanezumab approximates 5900 patient-years of treatment exposure.

A total of 17 clinical studies overall, (4 Phase 2 studies and 13 Phase 3 studies [10 controlled]), were initiated to provide evidence of efficacy and safety of tanezumab with intravenous (IV) or subcutaneous (SC) administration for the relief of the signs and symptoms of osteoarthritis alone or in combination with NSAIDs. Both IV and SC routes of administration with tanezumab at fixed dose levels of 2.5 mg, 5 mg, and 10 mg every 8 weeks were evaluated in Phase 3 clinical studies in patients with osteoarthritis.

In addition to the osteoarthritis studies, 11 Phase 1/2 studies were conducted to examine the efficacy and safety of tanezumab in other musculoskeletal, neuropathic, and visceral pain conditions and 2 Phase 2 studies in metastatic bone pain have been conducted. In these studies, tanezumab was administered by IV or SC administration every 8 weeks at fixed doses ranging from 1 mg to 20 mg or equivalent body-weight adjusted doses up to 100 mg.

In 2010, the US Food and Drug Administration's (FDA) Division of Analgesia, Anesthetic, and Addiction Products (DAAAP) placed tanezumab (June/July 2010) and subsequently the entire nerve growth factor inhibitor (NGFI) class (December 2010) on partial clinical hold due to adverse events initially described by investigators as osteonecrosis that in some cases resulted in total joint replacement. Pfizer voluntarily imposed the partial clinical hold on study conduct in all countries. The conduct of Phase 2/3 studies in osteoarthritis or other chronic pain conditions was impacted to varying extents by the partial clinical hold placed on the tanezumab clinical development program in June/July 2010.

Extensive analyses of the reports of osteonecrosis and other total joint replacements were conducted.<sup>1</sup> On March 12, 2012, the FDA Arthritis Advisory Committee reviewed these results as well as those prepared by the FDA.<sup>2,3</sup> The committee endorsed continued clinical development of the NGFI class of compounds with additional measures to minimize the risk and further protect subject safety. On August 28, 2012, the FDA lifted the partial clinical hold on tanezumab allowing the resumption of clinical studies for osteoarthritis and all other chronic pain conditions.

The FDA placed another partial clinical hold on the tanezumab clinical development program as well as all anti-NGF antibody studies in December 2012 due to concerns about adverse changes in the sympathetic nervous system of mature animals. Only studies in patients with cancer pain were allowed to continue. During 2013-2014, Pfizer conducted a comprehensive series of nonclinical studies to investigate the nonclinical effects on the sympathetic nervous system which led to the partial clinical hold (described in Section 5.3 of the tanezumab Investigators' Brochure).

In animal studies in rats and non-human primates (described in Section 5.3 of the tanezumab Investigators' Brochure), tanezumab treatment for up to 6 months, with doses producing greater systemic exposure than observed with clinical doses, was associated with lower sympathetic ganglion volume and lower average size of post-ganglionic sympathetic neurons when compared to control animals. All effects were completely reversible following a dosing-free recovery period. In a separate cardiovascular function study in non-human primates (described in Section 5.1 of the tanezumab Investigators' Brochure), functional

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changes in the cardiovascular system controlled by the sympathetic nervous system were not observed.

Although evidence of clinically important effects on the sympathetic nervous system have not been identified in previously completed tanezumab studies, per agreement with the FDA, this and other clinical studies of tanezumab will incorporate additional safety measures to monitor for and manage subjects who may develop evidence of clinically important sympathetic nervous system dysfunction.

### 1.2.3.1. Overview of Efficacy in Osteoarthritis Clinical Studies

Across the 3 co-primary measures of efficacy in four completed Phase 3 studies of tanezumab monotherapy (IV administration), doses of 2.5 mg, 5 mg, and 10 mg provided significant improvement over placebo treatment. All of the tanezumab doses tested were consistently efficacious. In Studies A4091011<sup>13</sup> and A4091014,<sup>14</sup> the degree of mean improvement across the three efficacy domains was similar and generally dose ordered with tanezumab 10 mg providing the greatest mean response in each of the studies 3 co-primary endpoint comparisons to placebo treatment although only small differences in the magnitude of response were evident among the three doses of tanezumab. In Studies A4091015<sup>15</sup> and A4091018,<sup>16</sup> tanezumab 5 mg provided modestly greater mean improvement over tanezumab 10 mg across most of the co-primary endpoints.

In each of these four studies, the mean Baseline WOMAC<sup>17</sup> Pain subscale scores exceeded 7 on a scale of 0 to 10 indicating a subject population with severe pain on average prior to study entry. The mean reduction in pain with tanezumab treatment was typically 3 points or greater yielding an improvement in pain on average from severe to nearly mild in severity. This reduction in pain was associated with equivalent improvements in function and global well being.

The clinical significance of the reduction in pain with tanezumab treatment was assessed by the evaluation of subject responder rates using a categorical assessment of the WOMAC Pain subscale results, the OMERACT-OARSI<sup>18</sup> (Outcomes Measures in Arthritis Clinical Trials Osteoarthritis Research Society International) Responder Index and a 2-grade or larger categorical improvement in the Patient's Global Assessment of Osteoarthritis. All responder analyses were determined with Baseline Observation carried Forward (BOCF) imputation unless otherwise noted.

In Studies A4091011 and A4091014, statistically significant response rates compared to placebo treatment were demonstrated at Week 16 with all tanezumab doses for the percentage of subjects with reductions in pain  $\geq 30\%$ ,  $\geq 50\%$ ,  $\geq 70\%$ , and  $\geq 90\%$  on the WOMAC Pain subscale in both studies with one exception (A4091011  $\geq 70\%$  reduction with tanezumab 2.5 mg vs placebo p-value was 0.053).

A prospectively defined analysis of subjects participating in Studies A4091011, A4091014, A4091015, or A4091018 was carried out to evaluate the efficacy of tanezumab with severe symptomatic osteoarthritis. Subjects defined with severe pain were those with a Baseline WOMAC Pain score  $\geq 7$  and a WOMAC Physical Function score of  $\geq 7$  and a score of "poor"

or “very poor” in the Patient’s Global Assessment of Osteoarthritis. Of the 2979 subjects enrolled across the 4 studies, 742 (25.1%) met these criteria for severe disease. Tanezumab 5 mg and 10 mg provided significant and clinically meaningful benefit in this severe subject cohort when compared to placebo treatment.

A key objective of Studies A4091015 and A4091018 was to compare the efficacy of tanezumab 5 mg and 10 mg versus naproxen 500 mg bid for the symptomatic treatment of osteoarthritis. To control the type 1 error rate for multiple comparisons, fixed sequence (step down) testing and the Hochberg procedure were predefined to begin with the highest dose (tanezumab 10 mg) followed by tanezumab 5 mg. As a result, despite replicate statistically significant differences with tanezumab 5 mg versus naproxen across 3 co-primary endpoints, a total of 6 comparisons, it is only possible to conclude statistically that tanezumab was superior to naproxen with respect to WOMAC Physical Function in both studies and the Patient’s Global Assessment of Osteoarthritis in one study.

In Study A4091030,<sup>19</sup> a key objective was to demonstrate that tanezumab 5 mg and tanezumab 10 mg administered by IV infusion were superior, or at a minimum non-inferior, to oxycodone controlled-release (CR) 10-40 mg administered every 12 hours in the treatment of osteoarthritis. This objective was achieved. All four comparisons were statistically significant at Week 8; non-inferiority of tanezumab 10 mg versus oxycodone CR, superiority of tanezumab 10 mg versus oxycodone CR ( $p=0.018$ ), non-inferiority of tanezumab 5 mg versus oxycodone CR, and superiority of tanezumab 5 mg versus oxycodone CR ( $p<0.001$ ). In this study, oxycodone CR failed to separate from placebo treatment across all response measures at Week 8. Treatment with tanezumab 10 mg did not provide additional efficacy benefit above that observed with tanezumab 5 mg treatment.

In the largest safety and efficacy study, Study A4091025,<sup>20</sup> the addition of tanezumab 5 mg or 10 mg (administered by IV infusion) to oral NSAID treatment (ie, celecoxib 100 mg BID or naproxen 500 mg BID) did not provide substantial efficacy benefit over tanezumab 5 mg or 10 mg monotherapy, respectively. Only two statistically significant treatment differences were observed among these co-primary endpoint comparisons.

### 1.2.3.2. Overview of Safety in Clinical Studies

Based on data from all subject populations who have received tanezumab in completed clinical studies to date, the adverse drug reactions listed in [Table 2](#) are considered to be expected in subjects who are treated with tanezumab.

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**Table 2. Adverse Drug Reactions in All Subjects Receiving Tanezumab**

System Organ Class	Adverse Drug Reactions	Frequency <sup>2</sup>
Nervous system disorders	Burning sensation Carpal tunnel syndrome Hyperesthesia Hypoesthesia Paresthesia	Common
	Allodynia Neuropathy peripheral	Uncommon
Musculoskeletal and connective tissue disorders	Rapidly Progressive Osteoarthritis <i>(in patients with underlying osteoarthritis<sup>1</sup>)</i>	Uncommon
	Arthralgia Joint swelling Myalgia Pain in extremity	Common
General disorders and administration site conditions	Oedema peripheral	Common
<sup>1</sup> Rapidly Progressive Osteoarthritis may occur in subjects with underlying osteoarthritis. The frequency is estimated from adjudicated events of rapidly progressive osteoarthritis in historic clinical studies of tanezumab, which did not include specific risk minimization measures for this adverse reaction. <sup>2</sup> Common (≥1% and <10%); Uncommon (≥0.1% and <1%).		

A total of 7491 subjects were treated in 9 controlled Phase 3 osteoarthritis studies. The majority of these subjects were treated in studies using IV administration of tanezumab; however, approximately 900 subjects were treated in 2 studies in subjects with osteoarthritis using SC administration. The adverse event profile of SC administration of tanezumab is comparable to the IV route based on the results of study A4091027 which compared SC versus IV administration in subjects with osteoarthritis. The incidence of adverse events, withdrawals due to adverse events, and serious adverse events in subjects treated with tanezumab monotherapy (5-10 mg) was similar to subjects receiving active comparator treatment and increased over placebo-treated subjects. In the tanezumab 2.5 mg monotherapy treatment group, the incidence of adverse events was similar to active comparator while the incidence of withdrawals due to adverse events, and serious adverse events was similar to that of the placebo treatment group. Across the tanezumab monotherapy doses, the rates of adverse events, withdrawals due to adverse events, and serious adverse events, were similar with tanezumab 5 mg and 10 mg, and elevated in comparison to tanezumab 2.5 mg. Tanezumab/NSAID combination therapy was associated with higher overall adverse event rates. The relationship of incidence to the dose of tanezumab administered was similar to that seen with tanezumab monotherapy.

Based on data from the Phase 3 osteoarthritis studies and results of an independent adjudication of investigator-reported adverse events of osteonecrosis and total joint replacements, the risk of rapidly progressive osteoarthritis with tanezumab treatment was greater than with placebo or active comparator treatment.

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Among the most frequently reported adverse events in the controlled Phase 3 osteoarthritis studies, the incidence of peripheral edema, upper respiratory tract infection, fall, arthralgia, back pain, joint swelling, pain in extremity, hypoesthesia, and paresthesia tended to be higher in subjects receiving tanezumab monotherapy than subjects receiving either placebo or active comparator treatment. The incidence of peripheral edema, arthralgia, joint swelling, pain in extremity, and paresthesia increased with increasing doses of tanezumab monotherapy. The adverse events with increased incidence observed with active comparator over tanezumab monotherapy included the following: constipation, nausea, urinary tract infection, nasopharyngitis, osteoarthritis, and hypertension.

The most common adverse events reported in the non-controlled, long-term Phase 3 osteoarthritis studies were similar to those seen in the controlled Phase 3 osteoarthritis studies with the exception of the inclusion of musculoskeletal pain and exclusion of hypertension and nasopharyngitis and all gastrointestinal-related adverse events. Dose-related increases in the incidence of peripheral edema, joint swelling, osteoarthritis and paresthesia were observed.

#### **1.2.3.2.1. Sympathetic Nervous System**

In completed Phase 3 osteoarthritis studies, the incidence and discontinuation rates due to adverse events consistent with decreased sympathetic function associated with tanezumab monotherapy (combined doses of 2.5 to 10 mg) were less than or equal to rates with placebo or active comparator. No evidence of dose related elevations in the frequency of adverse events suggestive of decreased sympathetic nervous system function were observed at doses of 2.5 to 10 mg in subjects with osteoarthritis. Tanezumab 20 mg in chronic low back pain had marginally higher event rates compared to placebo and active comparator treatment groups.

Based on completed osteoarthritis studies where orthostatic blood pressure, heart rate deep breathing, or autonomic symptoms captured with the Neuropathy Symptom Change (NSC) questionnaire were specifically assessed, the data are not suggestive of an adverse effect of tanezumab on autonomic function.

Although evidence of clinically important effects on the sympathetic nervous system have not been identified in previously completed tanezumab studies, per agreement with the FDA, this and other clinical studies of tanezumab will incorporate additional safety measures to monitor for and manage subjects who may develop evidence of clinically important sympathetic nervous system dysfunction.

### 1.2.3.3. Subcutaneous Administration of Tanezumab in Clinical Studies

The formulation of tanezumab that has been administered by SC injection is identical to what has been administered by IV infusion and is administered as a 1 mL SC injection in the thigh or abdomen. The safety and efficacy of tanezumab when administered by SC injection has been evaluated in OA subjects primarily in two studies, A4091027<sup>21</sup> and A4091043<sup>22</sup>, and in subjects with chronic low back pain in one study (A4091039<sup>23</sup>), all of which were impacted by the FDA-imposed clinical hold. A total of 1905 subjects were treated in these studies. The observed efficacy and safety profile of tanezumab administered SC was similar to IV administration.

Study A4091027<sup>21</sup> was designed as a randomized, placebo-controlled study to demonstrate the efficacy and safety of tanezumab 2.5 mg, 5 mg, or 10 mg SC administered at 8-week intervals and the therapeutic equivalence of tanezumab 10 mg SC and tanezumab 10 mg IV administered at 8-week intervals in subjects with osteoarthritis of the knee. Due to the clinical hold, enrollment was stopped prematurely and, therefore, was insufficient to yield adequate power to fulfill the primary objectives. The overall incidence of adverse events was comparable to that observed in previous tanezumab IV osteoarthritis studies, and with the exception of injection-site reactions, the adverse event profile was comparable to that of previous tanezumab IV studies in subjects with osteoarthritis. The higher incidence of injection-site reaction compared to other studies was likely due to the implementation of directed injection-site assessment – a procedure that was not a component of earlier tanezumab studies, which had included only IV administration of tanezumab. The majority of reported adverse events of injection-site reaction were mild, and none were severe. Across treatment groups, the incidence of serious adverse events and discontinuation due to adverse events was low.

Study A4091043<sup>22</sup> was a randomized, double-blind, parallel-group, multicenter long-term safety study of tanezumab when administered by SC injection in subjects with OA of the knee or hip. Approximately 600 subjects were to be entered into the study. All subjects were randomized to receive SC administration of tanezumab 2.5, 5, or 10 mg at 8-week intervals (7 doses total) for approximately 1 year (56 weeks). A total of 231, 222, and 226 subjects were assigned to tanezumab 2.5, 5, and 10 mg treatment groups, respectively; all of these subjects were treated with investigational product except for 1 subject in the tanezumab 2.5 mg treatment group who was randomized but not treated. No subjects completed the study as a result of the clinical hold. The overall incidence of adverse events (all causality) was dose responsive and was highest in the tanezumab 10 mg (80.1%) treatment group which was followed by successively lower incidences in the tanezumab 5 mg (76.1%) and 2.5 mg (68.7%) treatment groups. Overall and based upon a tendency toward greater incidences of adverse events, serious adverse events, all-cause total joint replacement, abnormalities in neurological examinations, and neurological consultation findings thought to be consistent with new or worsened peripheral neuropathy, the tanezumab 10 mg treatment group appeared to be less well tolerated relative to the tanezumab 2.5 and 5 mg dose levels.

#### 1.2.3.4. Joint Safety

Following the imposition of the clinical hold, a comprehensive investigation and analyses related to joint-safety were conducted, based on tanezumab monotherapy exposure in over 6400 subjects and tanezumab/NSAID combination therapy in 3400 subjects. There were over 5000 subjects who received tanezumab treatment alone or in combination with NSAIDs for 6 months or longer. The program was sufficient to define and characterize the adverse event of concern – rapidly progressive osteoarthritis – and evaluate the risk of rapidly progressive osteoarthritis in the context of the overall benefit-risk profile of tanezumab compared to standard of care. The results and conclusions regarding tanezumab and the other anti-NGF therapies are provided in detail elsewhere.<sup>1</sup>

After careful investigation, no evidence was found to substantiate that tanezumab is associated with an increased risk of osteonecrosis, a disease process quite distinct from osteoarthritis. A risk of rapidly progressive osteoarthritis was identified. The risk of rapidly progressive osteoarthritis with tanezumab monotherapy was well below that observed with tanezumab/NSAID combination therapy but greater than with placebo or active comparator treatment. A majority of subjects identified with rapidly progressive osteoarthritis had advanced osteoarthritis of the affected joint prior to treatment. The event rate of all-cause joint replacements in subjects with osteoarthritis was comparable among placebo, active comparator, and tanezumab monotherapy treatment groups.

Risk mitigation measures have been developed as an outgrowth of the joint-related safety analyses to reduce the risk of rapidly progressive osteoarthritis. Using recommendations from discussions with European agencies [United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA), Germany's Paul Ehrlich Institute (PEI) and Spain's Agency on Medicinal Products and Medical Devices (AEMPS)] as well as the FDA Arthritis Advisory Committee and interactions with FDA, risk mitigation measures were developed. These risk mitigation measures have been included in this study and are outlined as follows:

**Risk Minimization:** (1) exclude chronic concomitant NSAID use, (2) exclude tanezumab doses that have been explored and do not demonstrate benefit over lower doses in the condition under study, (3) exclude subjects with evidence of rapidly progressive osteoarthritis or risk factors for such from participating in clinical studies, (4) discontinue treatment with investigational product in subjects who fail to achieve adequate pain relief and (5) exclude subjects who are not suitable candidates for total joint replacement from study participation.

**Risk Identification and Management:** (1) evaluation and follow-up for severe persistent joint pain, (2) extended post-treatment follow-up, (3) a program-level Central Radiograph Reader and subject-level stopping criteria, (4) an Adjudication Committee, and (5) a Data Monitoring Committee and protocol-level stopping rules.

**Risk Characterization:** (1) Comprehensive evaluation of osteoarthritis medical history prior to study entry, (2) scheduled radiographic assessments during the studies, (3) Magnetic Resonance Imaging (MRI) scans, (4) Dual-energy X-ray Absorptiometry (DXA) scans

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(5) activity monitoring, (6) surgical and post-operative total joint replacement outcomes, and (7) biomarker determinations.

#### 1.2.3.4.1. Rapidly Progressive Osteoarthritis

Rapidly progressive osteoarthritis of the hip was first described by Forestier in 1957 and subsequently described in a number of studies as atrophic osteoarthritis, rapidly destructive osteoarthritis, rapidly destructive arthropathy, rapidly progressive hip disease, or rapidly destructive coxarthrosis.<sup>24-36</sup> Rapidly progressive hip osteoarthritis is characterized by subjects who typically present with hip pain, often severe, with radiographs that show rapid joint space narrowing as a result of chondrolysis from a prior radiograph and, subsequently, an osteolytic phase with severe progressive atrophic bone destruction involving the femoral head and the acetabulum. There can be marked flattening of the femoral head and loss of subchondral bone in the weight-bearing area and in some cases the femoral head appears sheared off. Osteophytes are typically conspicuously small or absent. Bone sclerosis is often present at sites of impaction of the femoral head and the acetabulum, subchondral detritus is invariably present and bone fragmentation and debris are commonly observed that can lead to synovitis. Lequesne proposed that subjects with 2 mm/year or greater of joint space narrowing or loss of more than 50% of the joint space within 1 year should be considered to have rapidly progressive osteoarthritis.<sup>26</sup> Due to a lack of longitudinal studies, it is not clear what proportion of subjects with rapid loss of joint space (chondrolysis) will progress to have bone destruction. Rapid progression of osteoarthritis has also been described in the shoulder and the knee.<sup>37,38</sup>

The incidence of rapidly progressive osteoarthritis in the overall osteoarthritis population is not well defined. For rapid progression of hip osteoarthritis, the prevalence ranges from approximately 2% to 18% based on clinical case series analyses.<sup>27,28,30,31,32,39</sup>

The pathophysiology of rapidly progressive osteoarthritis is not understood. Various mechanisms have been proposed including; ischemia, venous stasis, local nutritional deficiencies, synovitis, mechanical overloading, NSAID or corticosteroid use, intra-articular deposition of hydroxyapatite or pyrophosphate crystals and subchondral insufficiency fractures.<sup>29,32,36,40,41</sup>

One objective of the current study is to explore relationships between a variety of biomarkers (biochemical, physical activity level and radiographic) and joint safety events with an aim of further characterizing the pathophysiology of orthopedic events that may be observed in the study.

#### 1.2.4. Dose Selection Rationale

Intravenous and SC administration of tanezumab at doses of 2.5 mg, 5 mg and 10 mg was shown to reduce pain and improve function in a dose-related manner in Phase 3 studies of osteoarthritis. As one of the risk mitigation features identified through analysis of orthopedic safety and efficacy data, no further study of the tanezumab 10 mg dose will be conducted in subjects with osteoarthritis as this dose did not provide sufficient additional efficacy benefit over the 5 mg dose. Unlike the 10 mg dose which did not provide added efficacy benefit

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over the 5 mg dose, the 5-mg dose is expected to provide added efficacy benefit over the 2.5-mg dose. Based upon prior studies, this additional efficacy benefit is likely to be most evident in subjects considered to have severe symptomatic osteoarthritis as defined above in [Section 1.2.3.1](#).

The current study will investigate the safety and efficacy of fixed-dose levels of tanezumab 2.5 mg and 5 mg administered up to 7 times at 8-week intervals relative to an active comparator treatment group (NSAID). Subjects randomized to the active comparator treatment group will receive the NSAID they were receiving prior to study entry (naproxen, diclofenac ER or celecoxib). Subjects randomized to receive NSAID in the current study will receive them at protocol specified doses (naproxen 500 mg BID, diclofenac ER 75 mg BID or celecoxib 100 mg BID). These doses represent maximal or near maximal labeled doses used for the treatment of osteoarthritis.

Inclusion of the active comparator treatment group will allow the safety of tanezumab to be benchmarked against three common NSAIDs that are used in the treatment of pain associated with osteoarthritis. In particular, the long duration of this study necessitated the use of an active comparator rather than placebo. As no single NSAID is widely used across all geographic regions, inclusion of three different NSAIDs in a large study such as this will facilitate subject enrollment across geographic regions.

#### **1.2.5. Subject Population Selection Rationale**

The primary objectives of this study are: 1) to characterize the long term joint safety risks of tanezumab using a composite endpoint to include adjudication outcomes of rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture and 2) demonstrate the analgesic superiority of tanezumab relative to NSAID. The long duration of the current study precludes the use of a placebo control group and necessitates the use of an active control group that provides subjects with some degree of efficacy. To facilitate inclusion of an active control treatment group that will serve as a benchmark for evaluation of the long-term safety and efficacy of tanezumab, subjects entering the current study must have moderate to severe pain while receiving their current stable dosing regimen of oral NSAID therapy (naproxen, celecoxib, diclofenac, aceclofenac, ibuprofen, loxoprofen, meloxicam, nabumetone, sulindac or ketoprofen), be tolerating their NSAID regimen and be taking this medication regularly during the 30-day period prior to the Screening Visit.

To frame the risk of subjects experiencing joint safety events in this and other studies of tanezumab in subjects with osteoarthritis, Number Needed to Harm (NNH) estimates were calculated. The NNH estimates represent the number of subjects that would need to be in each treatment group, such that there would be one additional joint safety event in the tanezumab group compared to the active comparator group. The NNH estimates were based upon the incidence of joint safety events that formed a composite endpoint consisting of all-cause total joint replacement, adjudicated osteonecrosis, adjudicated rapidly progressive osteoarthritis and adjudicated subchondral insufficiency fracture. To show the potential impact of risk mitigation measures on event rates, NNH estimates were calculated using observed data and data considered to be representative of joint safety event rates that might

be seen after implementation of risk mitigation measures outlined in [Section 1.2.3.4](#). The NNH estimates are presented in Table 3 and suggest that with implementation of risk mitigation measures, the level of risk subjects may experience in this study is low and potentially lower (for the tanezumab 2.5 mg treatment group) than what a subject may experience during treatment with an active comparator.

**Table 3. Number Needed to Harm (NNH) Estimates for a Composite Joint Safety Endpoint<sup>1</sup> in Phase 3 Osteoarthritis Studies<sup>2</sup>**

	Observed Results			Results with Risk Mitigation Measures Applied		
	Tanezumab Overall	Tanezumab Monotherapy	Tanezumab + NSAID	Tanezumab Monotherapy		
Doses	2.5 mg – 10 mg	2.5 mg – 10 mg	2.5 mg – 10 mg	2.5 mg – 5 mg	2.5 mg	5 mg
N	6701	4273	3028	1578	396	1182
n (%)	76 (1.1)	23 (0.5)	53 (1.8)	4 (0.3)	0 (0)	4 (0.3)
NNH	102	263	63	**	**	2506

N = Number of subjects; n (%) = number (%) of subjects with a joint safety event; NNH = Number of subjects treated with tanezumab instead of active comparator to observe 1 additional joint safety event  
\*\*= Indicates that a negative number is needed to harm translating to a lower risk with tanezumab than with active comparator

<sup>1</sup> Includes all-cause total-joint replacement, adjudicated osteonecrosis or rapidly progressive osteoarthritis and subchondral insufficiency fracture

<sup>2</sup> A4091011, A4091014, A4091015, A4091016, A4091017, A4091018, A4091025, A4091026, A4091027, A4091030, and A4091043

To quantitate the benefit (pain relief) of treatment with tanezumab relative to active comparator, Number Needed to Treat (NNT) estimates were calculated using data from controlled Phase 3 osteoarthritis studies. The NNT represents the number of subjects that would need to be treated in each treatment group, such that there would be one additional responder in the tanezumab group compared to the active comparator group. Responders were defined as subjects who had a decrease from Baseline WOMAC pain score of  $\geq 50\%$ ,  $\geq 70\%$  or  $\geq 90\%$ . There were no Phase 3 osteoarthritis studies that included a tanezumab 2.5 mg monotherapy and an active comparator treatment group which precluded the ability to calculate an NNT for 2.5 mg monotherapy versus active comparator. The NNT values are presented in [Table 4](#).

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**Table 4. Number Needed to Treat (NNT) with Tanezumab versus NSAID in the Treatment of Osteoarthritis**

Number of subjects treated with tanezumab instead of active comparator <sup>1</sup> to observe 1 additional responder	Tanezumab Monotherapy <sup>2</sup>			Tanezumab + NSAID <sup>3</sup>		
	2.5 mg	5 mg N=852	10 mg N=858	2.5 mg N=157	5 mg N=686	10 mg N=687
WOMAC Pain ≥50% Response	—	10	10	27	8	6
WOMAC Pain ≥70% Response	—	9	11	29	11	7
WOMAC Pain ≥90% Response	—	20	22	26	21	14

<sup>1</sup> Active Comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac ER 75 mg BID.

<sup>2</sup> Efficacy determined by BOCF imputation at Week 16 landmark analysis for studies 1015, 1018, & 1025 combined.

<sup>3</sup> Efficacy determined by BOCF imputation at Week 16 landmark analysis for study 1017 alone (2.5 mg), or Studies 1017 & 1025 combined (5 mg and 10 mg).

Considering the risk mitigation measures that have been included in this study and the impact they may have on minimizing risk relative to the expected benefit as expressed in NNH and NNT estimates, respectively, the benefit vs. risk relationship for subjects in this study is expected to be positive (ie, favoring a benefit).

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Investigator’s Brochure. The Single Reference Safety Document (SRSD) for the comparator agents are the Company Core Data Sheet for celecoxib, the US Package Insert for naproxen (Amneal) and the Summary of Product Characteristics (UK) for diclofenac ER (Novartis).

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Objectives

#### Primary Objectives

- Characterize the long-term risk of joint safety events in subjects with osteoarthritis of the knee or hip who receive tanezumab 2.5 mg or tanezumab 5 mg SC versus NSAID treatment (naproxen 500 mg BID, celecoxib 100 mg BID, or diclofenac ER 75 mg BID) over the course of 56-weeks of treatment using a composite endpoint (includes adjudication outcomes of rapidly progressive osteoarthritis type-1 or type-2, subchondral insufficiency fracture (SPONK), primary osteonecrosis, or pathological fracture).
- Demonstrate superior efficacy of tanezumab 2.5 mg and tanezumab 5 mg SC versus NSAID treatment (naproxen 500 mg BID, celecoxib 100 mg BID, or diclofenac ER 75 mg BID) at Week 16.

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## Secondary Objectives

- Characterize the long-term joint safety risk using a composite endpoint (includes adjudication outcomes of rapidly progressive osteoarthritis (type-2 only), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture).
- Characterize the long-term risk of the following individual adjudication outcomes occurring: rapidly progressive osteoarthritis (type-1 only), rapidly progressive osteoarthritis (type-2 only), rapidly progressive osteoarthritis (type-1 or type-2 combined), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, and pathological fracture.
- Characterize the long-term risk of all-cause total joint replacements (subjects who undergo total joint replacement plus subjects who have an adjudicated outcome of rapidly progressive osteoarthritis type-1 or type-2, subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture whether they undergo total joint replacement or not) occurring.
- Characterize joint space width changes in subjects with Kellgren-Lawrence Grade 2 or 3 osteoarthritis of the index knee or index hip.
- Demonstrate superior efficacy of tanezumab 5 mg and tanezumab 2.5 mg SC versus each separate NSAID treatment group (naproxen 500 mg BID, celecoxib 100 mg BID and diclofenac ER 75 mg BID) at Week 16.
- Demonstrate the efficacy of tanezumab 2.5 mg and tanezumab 5 mg SC versus NSAID (combined) treatment at all time points to Week 56.
- Evaluate the long-term safety of tanezumab 2.5 mg and tanezumab 5 mg SC.
- Explore relationships between adjudicated outcomes of rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture and variables that may be associated with these orthopedic risks.
- Characterize changes in physical activity level.

## **2.2. Endpoints**

### **2.2.1. Primary Endpoints**

- Incidence of a predefined composite endpoint consisting of adjudication outcomes of rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture (primary composite endpoint).

The co-primary efficacy endpoints are:

- Change from Baseline to Week 16 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale.
- Change from Baseline to Week 16 in the WOMAC Physical Function subscale.
- Change from Baseline to Week 16 in the Patient's Global Assessment of Osteoarthritis.

*The Japanese Specific co-primary efficacy endpoints are:*

- *Change from Baseline to Week 16 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale.*
- *Change from Baseline to Week 16 in the WOMAC Physical Function subscale.*

## **2.2.2. Secondary Endpoints**

### **2.2.2.1. Bone and Joint Safety**

- Incidence of a predefined composite endpoint consisting of adjudication outcomes of rapidly progressive osteoarthritis (type-2 only), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture.
- Incidence of individual adjudication outcomes of rapidly progressive osteoarthritis (type-1 only), rapidly progressive osteoarthritis (type-2 only), rapidly progressive osteoarthritis (type-1 or type-2 combined), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, and pathological fracture.
- Incidence of all-cause total joint replacements (subjects who undergo total joint replacement plus subjects who have an adjudicated outcome of rapidly progressive osteoarthritis type-1 or type-2, subchondral insufficiency fracture (SPONK), primary osteonecrosis, or pathological fracture whether they undergo total joint replacement or not).

### **2.2.2.2. Radiographic**

- Change from Baseline to Week 56 and Week 80 in Medial or Lateral Minimum Joint Space Width of the index knee (for subjects with Kellgren-Lawrence Grade 2 or 3 medial or lateral osteoarthritis of the index knee).
- Change from Baseline to Week 56 and Week 80 in Minimum Joint Space Width of the index hip (for subjects with Kellgren-Lawrence Grade 2 or 3 osteoarthritis of the index hip).

- Incidence of subjects with progression of osteoarthritis in the index knee according to Bland and Altman method, at Week 56 and Week 80 (separately) (for subjects with Kellgren-Lawrence Grade 2 or 3 medial or lateral osteoarthritis of the index knee).
- Incidence of subjects with progression of osteoarthritis in the index hip according to Bland and Altman method, at Week 56 and Week 80 (separately) (for subjects with Kellgren-Lawrence Grade 2 or 3 osteoarthritis of the index hip).

### 2.2.2.3. Efficacy

- WOMAC Pain subscale change from Baseline to Weeks 2, 4, 8, 24, 32, 40, 48, 56 and Week 64.
- WOMAC Physical Function subscale change from Baseline to Weeks 2, 4, 8, 24, 32, 40, 48, 56 and Week 64.
- Patient's Global Assessment of Osteoarthritis change from Baseline to Weeks 2, 4, 8, 16 (*Japan only*), 24, 32, 40, 48, 56 and Week 64.
- OMERACT-OARSI responder index at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- Treatment Response: Reduction in the WOMAC Pain subscale of  $\geq 30\%$ ,  $\geq 50\%$ ,  $\geq 70\%$  and  $\geq 90\%$  at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- Cumulative distribution of percent change from Baseline in the WOMAC Pain subscale score to Week 16, 24, and 56 (endpoint for summary only).
- Treatment Response: Reduction in the WOMAC Physical Function subscale of  $\geq 30\%$ ,  $\geq 50\%$ ,  $\geq 70\%$  and  $\geq 90\%$  at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- Cumulative distribution of percent change from Baseline in the WOMAC Physical Function subscale score to Week 16, 24, and 56 (endpoint for summary only).
- Treatment Response: Improvement of  $\geq 2$  points in Patient's Global Assessment of Osteoarthritis at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- Average pain score in the index joint change from Baseline to Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40, 48, 56 and Week 64.
- WOMAC Stiffness subscale change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- WOMAC Average change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.

- WOMAC Pain Subscale Item: Pain When Walking on a Flat Surface, change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- WOMAC Pain Subscale Item: Pain When Going Up or Down Stairs, change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI:OA) impairment scores change from Baseline to Weeks 16, 24, 56 and 64.
- EuroQol 5 Dimension (EQ-5D-5L™) dimensions and overall health utility score at Baseline and Weeks 8, 16, 24, 40, 56 and 64.
- Treatment Satisfaction Questionnaire Medicine v.II (TSQM v.II) satisfaction with effectiveness, side effects and convenience, and overall satisfaction at Weeks 16 and 56.
- Patient Reported Treatment Impact Assessment-Modified (mPRTI) at Weeks 16 and 56.
- Incidence and Time to discontinuation due to Lack of Efficacy.
- Usage of rescue medication (incidence and number of days of use) during Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56 and Week 64.
- Usage of rescue medication (amount taken) during Weeks 2, 4, 8 and Week 16.
- Health Care Resource Utilization at Baseline and Weeks 64, and 80.

#### 2.2.2.4. Activity Level Monitoring

- Lower Extremity Activity Scale: change from Baseline to Weeks 4, 8, 16, 24, 56 and Week 80 (all subjects).
- Change from Baseline to Weeks 16 and 56 in average daily minutes of physical activity (a subset of subjects).
- Change from Baseline to Weeks 16 and 56 in average daily physical activity counts (a subset of subjects).
- Change from Baseline to Weeks 16 and 56 in average daily minutes of moderate to vigorous physical activity (a subset of subjects).
- Change from Baseline to Weeks 16 and 56 in average daily minutes of bouts (sustained) moderate to vigorous physical activity (a subset of subjects).
- Change from Baseline to Weeks 16 and 56 in average daily step count (a subset of subjects).

#### **2.2.2.5. General Safety**

- Adverse Events.
- Standard safety assessments (safety laboratory testing [chemistry, hematology], sitting vital signs, electrocardiogram (ECG; 12-lead).
- Orthostatic (supine/standing) blood pressure assessments.
- Survey of Autonomic Symptom scores.
- Neurologic exam (Neuropathy Impairment Score [NIS]).
- Anti-tanezumab antibody assessments.
- Physical examinations.

#### **2.2.3. Tertiary Endpoints**

##### **2.2.3.1. Pharmacokinetic and Pharmacodynamic**

- Plasma tanezumab concentrations.
- Serum NGF assessment.
- Serum and urine osteoarthritis biomarker concentrations.
- Synovial fluid NGF assessment (for a subset of subjects).
- Synovial fluid tanezumab concentrations (for a subset of subjects).

### **3. STUDY DESIGN**

This is a randomized, double-blind, active-controlled, multicenter, parallel-group Phase 3 study of the safety and efficacy of tanezumab when administered by SC injection for 56 weeks compared to NSAIDs in subjects with osteoarthritis of the knee or hip. Approximately 3000 subjects will be randomized to one of 3 treatment groups in a 1:1:1 ratio (N=1000/treatment group). Treatment groups will include:

1. SC placebo (to match tanezumab) once every 8 weeks (a total of 7 administrations) plus NSAID administered orally (PO) (naproxen 500 mg BID PO, celecoxib 100 mg BID PO, or diclofenac ER 75 mg BID PO) through Week 56.
2. Tanezumab 2.5 mg SC once every 8 weeks (a total of 7 administrations) plus placebo BID PO (to match naproxen, celecoxib or diclofenac ER) through Week 56.
3. Tanezumab 5 mg SC once every 8 weeks (a total of 7 administrations) plus placebo BID PO (to match naproxen, celecoxib or diclofenac ER) through Week 56.



**Table 5. Stratified Randomization Scheme**

Randomization Strata	NSAID Treatment Taken During Screening	Index joint	Most Severe Kellgren-Lawrence Grade
1	Naproxen	Hip	2
2	Naproxen	Hip	3
3	Naproxen	Hip	4
4	Naproxen	Knee	2
5	Naproxen	Knee	3
6	Naproxen	Knee	4
7	Celecoxib	Hip	2
8	Celecoxib	Hip	3
9	Celecoxib	Hip	4
10	Celecoxib	Knee	2
11	Celecoxib	Knee	3
12	Celecoxib	Knee	4
13	Diclofenac	Hip	2
14	Diclofenac	Hip	3
15	Diclofenac	Hip	4
16	Diclofenac	Knee	2
17	Diclofenac	Knee	3
18	Diclofenac	Knee	4

A minimum of 660 subjects (approximately 220/treatment group) taking each NSAID (naproxen, celecoxib or diclofenac) during Screening will be randomized into the study.

The study is designed with a total (post-randomization) duration of 80 weeks and will consist of three periods: Screening (up to a maximum of 37 days), Double-blind Treatment (56 weeks) and Safety Follow-up (24 weeks). The Screening period (beginning up to 37 days prior to Randomization) includes a Washout Period (lasting 2-30 days), if required, and an Initial Pain Assessment Period (the 7 days prior to Baseline [Day 1]; minimum of 3 days).

Prior to entering the study, subjects must be receiving a stable dosing regimen of oral NSAID therapy consisting of one of the NSAIDs presented in the following table, be tolerating their NSAID regimen and be taking this medication regularly (defined as an average of at least 5 days per week) during the 30-day period prior to the Screening visit.

**Table 6. Qualifying Pre-study NSAID Treatment Regimens**

NSAID	Qualifying Dose Range
Naproxen	440 mg/day* to 1000 mg/day
Celecoxib	200 mg/day (either 100 mg BID or 200 mg QD)
Diclofenac	100 mg/day to 150 mg/day
Aceclofenac	200 mg/day
Loxoprofen	120 mg/day to 180 mg/day
Ibuprofen	1200 mg/day to 3200 mg/day
Meloxicam	5 mg/day to 15 mg/day
Nabumetone	1000 mg/day to 2000 mg/day
Sulindac	200 mg/day to 400 mg/day
Ketoprofen	200 mg/day

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\*A minimum dose of 440 mg/day is applicable for naproxen formulations that include the sodium salt of naproxen otherwise the minimum qualifying dose of naproxen is 500 mg/day

The Screening period will include the discontinuation and washout of all prohibited pain medications for at least 5 times the elimination half-life as well as the time needed to obtain confirmation of subject radiographic eligibility for the study from the Central Reader. The Screening period is a minimum of 2 or 3 weeks (14 to 21 days) to ensure subjects are on a stable regimen of study provided NSAID for at least 2 or 3 weeks prior to randomization. The length of the NSAID regimen stabilization period will depend on the NSAID subjects are receiving in the 30 days prior to screening. The NSAID regimen stabilization period will be a minimum of 2 weeks if the pre-study NSAID is celecoxib, naproxen or diclofenac or a minimum of 3 weeks if the pre-study NSAID is aceclofenac, loxoprofen, ibuprofen, meloxicam, nabumetone, sulindac, or ketoprofen. The minimum washout period is 2 days (48 hrs) for all prohibited pain medications that have an elimination half-life of less than 10 hours. The washout of prohibited pain medication may occur in parallel with the 2 or 3-week NSAID regimen stabilization. During the Washout Period, subjects will be provided with rescue medication (acetaminophen/paracetamol) that may be taken, if necessary, up to the maximum daily dose of 3000 mg per day. Use of rescue medication must be discontinued at least 24 hours prior to the Baseline (Randomization) Visit.

At the Screening visit, all subjects who were receiving celecoxib, diclofenac or naproxen prior to Screening will be provided with this same NSAID for use during the remainder of the Screening period and will be stabilized on an NSAID dosing regimen of celecoxib 100 mg BID, naproxen 500 mg BID, or diclofenac ER 75 mg BID for at least the final 2 weeks of the Screening period directly prior to the Baseline (Randomization/Day 1) visit.

All subjects who were receiving aceclofenac, loxoprofen, ibuprofen, meloxicam, nabumetone, sulindac or ketoprofen prior to Screening will be assigned to celecoxib, naproxen or diclofenac. The specific NSAID that subjects will be assigned to (celecoxib, naproxen or diclofenac) will be the choice of the investigator. Subjects will use this NSAID for the remainder of the Screening period and will be stabilized on a dosing regimen of celecoxib 100 mg BID, naproxen 500 mg BID, or diclofenac ER 75 mg BID for at least the final 3 weeks of the Screening period directly prior to the Baseline (Randomization/Day 1) visit.

During NSAID regimen stabilization, all subjects will be expected to maintain a minimum compliance of 70% (average of 5 of 7 days per week). Beginning at Screening, subjects should use study-supplied oral investigational product (NSAID during Screening and NSAID or matching placebo post-randomization) through Week 56.

The Screening period will include collection of radiographs of each knee, hip, and shoulder. All X-rays will be evaluated by a Central Reader to determine the radiographic eligibility of subjects for the study. Other major joints exhibiting signs or symptoms suggestive of osteoarthritis should also be imaged. A major joint is defined as a mobile synovial joint in the limbs such as shoulders, elbows, wrists, hips, knees, ankles and excluding the joints of the toes and hands. Screening X-rays should be obtained as early as possible in the Screening period to facilitate completion of all required screening procedures within the

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37-day Screening period. During Screening, subjects will also provide a pain score (scored with an 11-point numerical rating scale [NRS]) via Interactive Response Technology (IRT) for bilateral shoulders, hips and knees and any other major joint for which a radiograph is obtained (refer to [Section 7.3.4](#)).

Subjects who have been determined to be eligible from a radiographic (as determined by the Central Reader) and general screening procedure perspective (laboratory, ECGs, history etc.) will have MRIs of each hip and knee obtained prior to the Baseline (Day 1) visit. In addition, DXA scans will be obtained in subjects meeting National Osteoporosis Foundation recommendations for bone mineral density testing (refer to [Section 7.3.12](#) and [Appendix 10](#)). These procedures will likely occur in parallel with washout of prohibited pain medications and the 2-week period of pre-randomization NSAID regimen stabilization and must be completed prior to the Baseline (Day 1) visit.

Subjects at selected sites (to recruit approximately 360 subjects) will also have physical activity monitored via actigraphy over the course of 7 consecutive days during the Screening period. The activity monitoring will take place once subjects have been determined to be eligible from a radiographic (as determined by the Central Reader) and general screening procedure perspective (laboratory, ECGs, history etc.). Activity monitoring via actigraphy will be completed prior to the Baseline (Day 1) visit and will likely occur in parallel with washout of prohibited pain medications, the 2-week period of pre-randomization, NSAID regimen stabilization and collection of MRIs and DXA scans (if applicable).

Eligible subjects who have completed washout of prohibited pain medications and all other screening (Stage 1) assessments may begin the Initial Pain Assessment Period (IPAP). During the IPAP, the daily average pain score in the index joint (scored with an 11-point numerical rating scale [NRS]) and rescue medication use by subjects will be collected via IRT. Pain in major non-index joints will also be assessed once during the IPAP. The IPAP will begin approximately 7 days prior to the Baseline (Day 1) randomization visit. During the IPAP, subjects must complete at least 3 daily diary entries (joint pain and rescue medication use). Accelerometry (if applicable), MRI and DXA (if applicable) may be performed in parallel with the IPAP.

Those subjects who qualify at the Baseline (Day 1) visit will be randomized to 1 of 3 treatment groups.

Tanezumab 2.5 mg, 5 mg, or placebo for tanezumab will be administered as a SC injection and subjects will be observed for adverse events including signs and symptoms of hypersensitivity in the clinic for a minimum of 1 hour after each administration of investigational product. Subjects will take their first oral dose of NSAID (naproxen 500 mg BID, celecoxib 100 mg BID, or diclofenac ER 75 mg BID) or matching placebo of the Double-blind Treatment period in the evening on Day 1 (ie, a morning dose of oral double-blind, investigational product will not be taken). Additional administrations of SC investigational product will occur every 8 weeks following the Baseline (Day 1) administration through Week 48. Oral investigational product (NSAID or matching placebo) will be self-administered by subjects BID through Week 56 of the study. Efficacy, activity

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level and safety assessments will be conducted during clinic visits between Weeks 2 and 64. In addition, subjects will be contacted by telephone every 8 weeks between Weeks 12 and 60 and every 4 weeks between Weeks 64 and 80 (ie, Weeks 68, 72 and 76).

At the Week 16 visit, subjects must have a 30% or greater reduction in WOMAC Pain subscale relative to Baseline in the index joint and a 15% or greater reduction in WOMAC Pain subscale from Baseline at either Week 2, 4 or 8 in order to continue investigational product. Subjects who do not meet these response criteria will be discontinued from the Treatment Period and enter the 24-week Early Termination Follow-up period.

At Weeks 24, 56, and 80, all subjects will undergo repeat radiographs of each knee, hip and shoulder as well as any additional joint(s) that was imaged at Screening. At Week 24, confirmation of the continuing radiographic eligibility of subjects must be received from the Central Reader prior to administration of the Week 24 SC investigational product. Subjects with Kellgren-Lawrence Grade 3 or 4 osteoarthritis in any knee or hip joint, on the basis of the Central Reader's assessment of the screening X-rays, will have follow-up MRIs of each hip and knee obtained at Weeks 24, 56, and 80.

With the completion of the Double-blind Treatment period at the Week 56 visit, subjects will begin the 24-week Safety Follow-up period and will be asked to return to the clinic for 2 additional study visits. At Week 64 (16 weeks after the last dose of investigational product) efficacy assessments, adverse event and concomitant medication information will be collected and standard of care medication may be initiated. At the end of the 24-week Safety Follow-up period, subjects will return for a final study visit at Week 80 (End of Study). At the Week 80 visit, all End of Study procedures are to be completed. Between Weeks 64 and 80 in the Safety Follow-up period, subjects will be contacted by clinical research site staff at approximately monthly intervals to collect adverse event, concomitant drug and concomitant non-drug data.

Continuing on from the Initial Pain Assessment Period, subjects will provide a daily assessment of their index joint pain through Week 16 via IRT. Between Weeks 16 and 80 (End of Study), subjects will provide pain scores in the index joint weekly via IRT using a 24-hour recall period. Subjects will also provide a weekly assessment of their non-index joint (major joints, refer to [Section 7.1.1](#)) pain via IRT using a 24-hour recall period from the Initial Pain Assessment Period to Week 80. The use of rescue medication (acetaminophen/paracetamol) will be collected daily via IRT beginning in the IPAP to the Week 16 visit and then weekly until Week 80. On a weekly basis between Baseline and Week 80, subjects will record the number of days of concomitant NSAID (outside of oral investigational product) use via IRT.

Subjects who complete the Week 56 visit will be considered to have completed the Double-blind Treatment period and will enter the 24-week Safety Follow-up period. Subjects who have completed the Double-blind Treatment period and have entered the 24-week Safety Follow-up period and complete the Week 80 visit will be considered to have completed the study. Subjects who discontinue study treatment prior to completing the Week 56 visit will not be considered to have completed the Double-blind Treatment period.

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Subjects who do not complete the Double-blind Treatment period but who enter and complete the 24-week Early-termination follow-up period will be considered to have completed the study while those subjects who do not complete the 24-week Early-termination follow-up period, will not be considered to have completed the study.

Subjects who are discontinued from treatment prior to Week 56, either at their request or at the decision of the investigator, will be required to undergo 24 weeks of follow-up (referred to as Early Termination Follow-Up). The 24 weeks of follow-up will be obtained through 3 clinic visits and monthly phone calls to yield 24-weeks of post-treatment follow-up. In addition, subjects will be asked to continue to enter pain scores for index joints (and non-index joints when applicable) via IRT, weekly, through the end of the 24-week follow-up period. Subjects who have entered the Early Termination Follow-up period will also be asked to record weekly rescue medication and concomitant NSAID use via IRT.

Radiographs of each shoulder, knee and hip (and any other major joint imaged at Screening or identified as at risk [refer to [Section 7.4.4](#)] during the study) should be performed as soon as possible after the decision to withdraw from the study has been made, provided at least 30 days have passed since the last set of X-rays were collected. Subjects that were determined to have Kellgren-Lawrence Grade 3 or 4 osteoarthritis in any knee or hip joint at Screening should also have an MRI of each knee and hip performed. The remainder of efficacy and safety assessments should be done at the scheduled first visit which is to occur approximately 8 weeks after the last dose of SC investigational product (as described in [Section 6.4.1.1](#)). The site should also schedule the subject for two additional clinic visits. The second visit should be scheduled to occur approximately 16 weeks after the subject's last dose of SC investigational product (which corresponds to more than 5 times the elimination half-life of tanezumab) to collect safety and efficacy data (as described in [Section 6.4.1.3](#)). Once the clinic visit 16-weeks after the last administration of SC investigational product has been completed and final efficacy assessments have been collected, standard of care treatment will be offered to subjects for the remaining 8 weeks of the required Safety Follow-up period. Standard of care treatment may be initiated as needed and should be recorded on the concomitant medication Case Report Form (CRF). The third and final clinic visit should be scheduled to take place approximately 24-weeks after the subject received the last dose of SC investigational product. That visit (as described in [Section 6.4.1.5](#)), will include repeat radiographs of each shoulder, knee and hip (and any other major joint imaged at Screening or identified as at risk during the study) providing at least 30 days have elapsed since the last radiographs were obtained. Subjects that were determined to have Kellgren-Lawrence Grade 3 or 4 osteoarthritis in any knee or hip joint at Screening should also have an MRI of each knee and hip performed. Every effort should be made to have the subject agree to complete the entire 24-week Early Termination Safety Follow-up described above.

In the event a subject refuses to enter the Early Termination Safety Follow-up, or chooses to discontinue during the regularly planned Safety Follow-up period (after Week 56 and through Week 80), a complete early termination visit should be performed. This early termination visit should include all procedures scheduled for the Week 64 and Week 80 visits, unless the Week 64 visit has already been completed; in that case, only Week 80

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procedures will be required. In addition, if the Week 56 visit was not completed prior to termination, a general physical examination, body weight, WPAI:OA, EQ-5D-5L, TSQM v.II, and mPRTI will also be obtained. Females of childbearing potential will be advised to continue their contraception regimen during a period of 112 days (16 weeks) after the last dose of SC investigational product.

#### 4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

##### 4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
2. Male or female of any race,  $\geq 18$  years of age.
3. A diagnosis of osteoarthritis of the index hip or knee based on American College of Rheumatology criteria with X-ray confirmation (a Kellgren-Lawrence<sup>42</sup> X-ray Grade of  $\geq 2$  as diagnosed by the Central Reader; [Appendix 1](#)).
4. Subjects must meet the following criteria pertaining to their osteoarthritis treatment regimen:
  - Documented history indicating that acetaminophen therapy has not provided sufficient pain relief;
  - Currently receiving a stable dose regimen of oral NSAID therapy consisting of one of the NSAIDs presented in the following table, be tolerating this NSAID and be taking this medication regularly (defined as an average of at least 5 days per week) during the 30 day period prior to the Screening visit.):

**Table 7. Qualifying Pre-study NSAID Treatment Regimens**

NSAID	Qualifying Dose Range
Naproxen	440 mg/day* to 1000 mg/day
Celecoxib	200 mg/day (either 100 mg BID or 200 mg QD)
Diclofenac	100 mg/day to 150 mg/day
Aceclofenac	200 mg/day
Loxoprofen	120 mg/day to 180 mg/day
Ibuprofen	1200 mg/day to 3200 mg/day
Meloxicam	5 mg/day to 15 mg/day
Nabumetone	1000 mg/day to 2000 mg/day
Sulindac	200 mg/day to 400 mg/day
Ketoprofen	200 mg/day

\*A minimum dose of 440 mg/day is applicable for naproxen formulations that include the sodium salt of naproxen otherwise the minimum qualifying dose of naproxen is 500 mg/day

- Maintain a stabilized dose regimen of either naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac ER 75 mg BID (provided at Screening) with a minimum compliance of 70% (ie, 5 of 7 days per week) for the final 2 or 3 weeks of the Screening period directly prior to the Baseline (Day 1) visit.

AND at least 1 of the following criteria:

- Documented history indicating that tramadol treatment has not provided adequate pain relief or subject is unable to take tramadol due to contraindication or inability to tolerate;
  - Documented history indicating that opioid treatment has not provided adequate pain relief or subject is unwilling to take opioids, or unable to take opioids due to contraindication or inability to tolerate.
5. WOMAC Pain subscale NRS  $\geq 5$  in the index knee or index hip at Screening.
  6. Be willing to discontinue all non-study pain medications for osteoarthritis and not use prohibited pain medications throughout the duration of the study except as permitted per protocol.
  7. Female subjects of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for 112 days (16 weeks) after the last dose of assigned subcutaneous investigational product.

**NOTE:** In Japan, female subjects must not be of childbearing potential to be eligible for this study.

8. Female subjects who are not of childbearing potential (i.e, must meet at least one of the following criteria):
  - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

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- Have medically confirmed ovarian failure; or
  - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.
9. Subjects who are willing and able to comply with lifestyle guidelines, scheduled visits, treatment plan, laboratory tests, and other study procedures through the End of Study visit.

#### 4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.
2. Body Mass Index (BMI) of  $>39 \text{ kg/m}^2$ . For subjects requiring DXA scan (refer to [Section 7.3.12](#)) body weight  $\geq 300$  lbs is exclusionary.
3. History of other disease that may involve the index joint including inflammatory joint disease such as rheumatoid arthritis, seronegative spondyloarthropathy (eg, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease related arthropathy), crystalline disease (eg, gout or pseudogout), endocrinopathies, metabolic joint diseases, lupus erythematosus, joint infections, Paget's disease, or tumors.
4. Radiographic evidence of any of the following conditions in any screening radiograph as determined by the central radiology reviewer and as defined in the tanezumab program imaging atlas: excessive malalignment of the knee, severe chondrocalcinosis; other arthropathies (eg, rheumatoid arthritis), systemic metabolic bone disease (eg, pseudogout, Paget's disease, metastatic calcifications), large cystic lesions, primary or metastatic tumor lesions, stress or traumatic fracture.
5. Radiographic evidence of any of the following conditions as determined by the central radiology reviewer and as defined in the tanezumab program imaging atlas at Screening: 1) rapidly progressive osteoarthritis, 2) atrophic or hypotrophic osteoarthritis, 3) subchondral insufficiency fractures, 4) spontaneous osteonecrosis of the knee (SPONK), 5) osteonecrosis, or 6) pathologic fracture.
6. A history of osteonecrosis or osteoporotic fracture (ie, a subject with a history of osteoporosis and a minimally traumatic or atraumatic fracture).

7. History of significant trauma or surgery to a knee, hip or shoulder within the previous year.
8. Planned surgical procedure during the duration of the study.
9. Largely or wholly incapacitated, (eg, subject bedridden or confined to a wheelchair, permitting little or no selfcare).
10. Fibromyalgia, regional pain caused by lumbar or cervical compression with radiculopathy or other moderate to severe pain that may confound assessments or self-evaluation of the pain associated with osteoarthritis. Subjects with a present (current) history of sciatica are not eligible for participation. Subjects with a past history of sciatica who have been asymptomatic for at least one year and who have no evidence of radiculopathy or sciatic neuropathy on thorough neurologic examination are eligible participation.
11. A past history of carpal tunnel syndrome (CTS) with signs or symptoms of CTS in the one year prior to Screening.
12. Considered unfit for surgery, defined as Grade >3 on the American Society of Anesthesiologists (ASA) physical classification system for surgery (refer to [Appendix 2](#)), or subjects who would not be willing to undergo joint replacement surgery if required.
13. Contraindications to magnetic resonance imaging (refer to [Appendix 11](#), and Reference <sup>59</sup>).
14. History of intolerance or hypersensitivity to the relevant oral NSAID (naproxen, celecoxib or diclofenac) the subject could be randomized to receive or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of this NSAID is contraindicated (refer to product labeling).
15. History of intolerance or hypersensitivity to acetaminophen (paracetamol) or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of acetaminophen is contraindicated (refer to product labeling).
16. Use of prohibited medications without the appropriate washout period (if applicable) prior to Screening or Initial Pain Assessment Period (refer to [Section 5.8.1](#)).
17. Oral or intramuscular corticosteroids within 30 days prior to the IPAP.
18. Intra-articular corticosteroid injection in the index joint within 12 weeks, or to any other joint within 30 days prior to the IPAP.
19. Intra-articular hyaluronic acid injection in the index joint within 30 days (or within 18 weeks for long-acting formulations such as Synvisc) prior to the IPAP.

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20. History of cancer within 5 years prior to Screening, except for cutaneous basal cell or squamous cell cancer resolved by excision.
21. Signs and symptoms of clinically significant cardiac disease including but not limited to:
  - Ischemic cardiac disease (eg, unstable angina, myocardial infarction) in the 6 months prior to Screening;
  - Surgery or stent placement for coronary artery disease in the 6 months prior to Screening;
  - New York Heart Association (NYHA) Class III or IV congestive heart failure or known left ventricular dysfunction with ejection fraction  $\leq 35\%$ , cardiomyopathy, myocarditis in the 6 months prior to Screening;
  - Resting tachycardia (heart rate  $\geq 120$ ) or resting bradycardia (heart rate  $\leq 45$ ) on ECG at Screening;
  - QTcF interval  $> 500$  msec in the absence of confounding factors like bundle branch block or paced rhythm at Screening;
  - Any other cardiovascular illness that in the opinion of the Investigator would render a subject unsuitable to participate in the study;
  - Subjects with a history of heart block requiring ongoing treatment or that is associated with symptoms.
22. Diagnosis of a transient ischemic attack in the 6 months prior to Screening, diagnosis of stroke with residual deficits (eg, aphasia, substantial motor or sensory deficits), that would preclude completion of required study activities.
23. History, diagnosis, or signs and symptoms of clinically significant neurological disease, including but not limited to:
  - Alzheimer's disease or other types of dementia;
  - Clinically significant head trauma within the past year;
  - Peripheral or autonomic neuropathy;
  - Multiple sclerosis;
  - Epilepsy or seizure disorder with history of seizure within the last 2 years;
  - Myopathy.

24. History, diagnosis, signs or symptoms of any clinically significant psychiatric disorder, including but not limited to:
- Psychotic disorders;
  - Somatoform disorders;
  - Bipolar disorders;
  - Hospital admission for depression or suicide attempt within 5 years of Screening, or active severe major depression at Screening (determined from medical history: if needed, severity of depression may be assessed using the Patient Health Questionnaire [PHQ-9]).<sup>43</sup> A score of  $\geq 15$  on questions 1-9 of the PHQ-9 corresponds to severe depression. Refer to [Appendix 9](#));
  - Any other psychiatric illness that in the opinion of the Investigator would render a subject unsuitable to participate in the study.
25. History of known alcohol, analgesic or drug abuse within 2 years of Screening.
26. Previous exposure to exogenous NGF or to an anti-NGF antibody.
27. History of allergic or anaphylactic reaction to a therapeutic or diagnostic monoclonal antibody or IgG-fusion protein.
28. Resting, sitting blood pressure (BP)  $\geq 160$  mm Hg in systolic pressure or  $\geq 100$  mm Hg in diastolic pressure at Screening. If a subject is found to have untreated significant hypertension at Screening and antihypertensive treatment is initiated, assessment for study eligibility should be deferred until BP and antihypertensive medication have been stable for at least one month. For subjects with previously diagnosed hypertension, antihypertensive medications must be stable for at least 1 month prior to Screening.
29. Subjects who have evidence of orthostatic hypotension based upon replicate orthostatic blood pressure measurements (refer to [Section 7.3.5.1](#)). If orthostatic blood pressure change is not able to be determined (eg, unable to establish a stable supine systolic and diastolic blood pressure) then subject is not eligible for the study.
30. Subjects with a total impact score of  $>7$  on the Survey of Autonomic Symptoms (SAS), See [Appendix 15](#).
31. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $\geq 3.0$  times the upper limit of normal, or creatinine exceeding 1.7 mg/dL (150  $\mu\text{mol/L}$ ) in men or 1.5 mg/dL (133  $\mu\text{mol/L}$ ) in women, or hemoglobin A1c  $\geq 10\%$  at Screening. Repeat confirmatory tests may be performed.

32. Presence of drugs of abuse (including prescription medications without a valid prescription), or illegal drugs in the urine toxicology screen obtained at Screening.
33. Positive Hepatitis B, Hepatitis C, or Human Immunodeficiency Virus (HIV) tests at Screening indicative of current infection.
34. Participation in other studies involving investigational drug(s) (Phases 1-4) within 30 days (or 90 days for biologics) before Screening.
35. Pregnant female subjects; breastfeeding female subjects; female subjects of childbearing potential who are unwilling or unable to use two (2) highly effective methods of contraception as outlined in this protocol for the duration of the study and for 112 days (16 weeks) after last dose of investigational product.
36. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

#### 4.3. Randomization Criteria

In addition to meeting all inclusion and exclusion criteria requirements listed above, there are requirements for the following to be met before randomization can be called into the IRT system at the Baseline visit:

1. Subject must have completed appropriate washout of analgesics.
2. Subject must have made at least 3 pain diary entries in the 7 days prior to the Baseline (Day 1) visit.
3. Subject must have maintained a stabilized dose regimen of either naproxen 500 mg BID, celecoxib 100 mg BID or diclofenac ER 75 mg BID (depending on the subject's pre-study NSAID) with a minimum compliance of 70% (ie, 5 of 7 days per week) for at least the final 2 or 3 weeks of the Screening period directly prior to the Baseline (Day 1) visit.

*NOTE: In Japan, all subjects will maintain a stabilized dose regimen of celecoxib as defined above.*

4. Subject must have abstained from taking rescue medication (acetaminophen/paracetamol) within the 24 hours that precede dosing.
5. WOMAC Pain and Physical Function subscales NRS  $\geq 5$  in the index knee or index hip at Baseline.
6. Patient's Global Assessment of Osteoarthritis must be "fair", "poor," or "very poor" at Baseline.

7. Review of the ECG and laboratory results and confirmation that there are no clinically significant or exclusionary findings.
8. Subject must have had required Baseline X-rays, MRI and DXA (if appropriate) scan(s) obtained.
9. The index joint should be the most painful joint with a qualifying WOMAC Pain score and Kellgren-Lawrence Grade as confirmed by the Central Reader.
10. *In Japan, confirm female subjects are not of childbearing potential.*

#### 4.4. Life Style Guidelines

Subjects should maintain their normal daily routine, including stable doses of permitted medications and exercise program. Subjects are also permitted to continue with non-pharmacologic activities (eg, massage, physical therapy) during the trial. Subjects should be cautioned against initiating or altering strenuous exercise regimens during the study as this may influence efficacy and laboratory results. Subjects will be advised to avoid elective surgery (eg, oral surgery) during the course of the study if possible; the study clinician should be contacted for discussion prior to the surgery whenever possible. Subjects who undergo joint replacement or arthroplasty will be discontinued from investigational product and followed as described in [Section 6.4.2](#).

Refer to [Sections 5.8.1](#), [5.8.2](#) and [Appendix 3](#) for guidance on permitted and prohibited medications.

All female subjects who, are of child-bearing potential and are sexually active and at risk for pregnancy, must agree to use two (2) methods of highly effective contraception consistently and correctly for the duration of the active treatment period and for 112 days (16 weeks) after the last dose of SC investigational product. The investigator or his/or her designee, in consultation with the subject, will confirm the subject has selected the most appropriate forms of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least two of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the [Schedule of Activities](#) and document such conversation in the subject's chart. In addition, the investigator or his/or her designee will instruct the subject to call immediately if the selected contraception methods are discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected, implanted, or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same

treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

#### **4.5. Sponsor Qualified Medical Personnel**

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact center number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

#### **5. STUDY TREATMENTS**

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

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### 5.1. Allocation to Treatment

Subjects will be randomized at Baseline to one of the following treatment groups, all subjects will receive SC and PO treatment during the Double-blind Treatment period of the study:

**Table 8. Study Treatments**

Treatment Group	Subcutaneous Investigational Product (SC)	Oral Investigational Product (PO)*
1	Placebo for tanezumab once every 8 weeks x 7 doses	Naproxen 500 mg BID, celecoxib 100 mg BID, or diclofenac ER 75 mg BID through Week 56
2	Tanezumab 2.5 mg once every 8 weeks x 7 doses	Placebo for BID naproxen, BID diclofenac ER or BID celecoxib through Week 56
3	Tanezumab 5 mg once every 8 weeks x 7 doses	Placebo for BID naproxen, BID diclofenac ER or BID celecoxib through Week 56

\*In Japan, the oral investigational product will consist of celecoxib 100 mg BID or matching placebo for celecoxib BID

Subjects will be randomly assigned in a 1:1:1 ratio to the above treatment regimens according to a computer generated randomization schedule. As detailed in [Section 3](#), randomization will be stratified by index joint, most severe Kellgren-Lawrence grade (of any knee or hip joint) and NSAID treatment at study entry. Randomization will be coordinated centrally through Interactive Response Technology (IRT). The system will provide subject identification numbers at Screening, which will subsequently be linked to the treatment assignments at Randomization. The randomization code will be securely maintained by a person(s) who is independent of the trial conduct and produces the randomization code. It is the responsibility of the Principal Investigator to ensure that the subject is eligible for participation in the study before requesting Randomization. The study site will obtain the subject's randomization number and dispensable unit identification numbers (ie, the drug supply to be administered or supplied to subjects at relevant study visits) from the IRT. Further details will be provided in the Pharmacist Manual.

### 5.2. Breaking the Blind

This is a randomized, double-blind, active-controlled, parallel group study. The subjects, Investigators, Study Coordinators, clinical site staff, Clinical Research Associate (CRA), and staff directly involved with the study at Pfizer and its designees will be blinded to subject assignment.

Blinding should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

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### 5.3. Subject Compliance

Tanezumab and NSAID (celecoxib 100 mg, naproxen 500 mg, diclofenac 75 mg ER) or corresponding placebo (SC or PO) dosing will be recorded on the appropriate CRF. Because tanezumab or corresponding placebo will be administered by site staff, subject compliance with SC treatment is not anticipated to be an issue.

For oral NSAID treatments (celecoxib, naproxen, diclofenac ER or corresponding placebo) and rescue medication (acetaminophen / paracetamol), compliance will be reviewed and reconciled at each study visit. For oral investigational product (NSAID or matching placebo), investigators should encourage subjects to maintain 100% compliance. If a subject's overall compliance with oral investigational product falls to <70% in an 8 week dosing interval, the investigator will counsel the subject on the importance of good compliance and document efforts to improve the subject's compliance. The use of non-study NSAIDs is prohibited during the study except as described in [Section 5.8](#).

Protocol rules governing the use of rescue medication are described in [Section 5.8.2](#).

### 5.4. Drug Supplies

#### 5.4.1. Dosage Form(s) and Packaging

Tanezumab, placebo for tanezumab, NSAID (celecoxib, naproxen and diclofenac ER) and placebo for NSAID will be supplied by the Sponsor or designee.

##### 5.4.1.1. Tanezumab

Tanezumab 2.5 mg is presented as a sterile solution for subcutaneous administration, in a glass pre-filled syringe (PFS). Each PFS contains a sufficient amount of tanezumab to provide the intended dose of drug at a concentration of 2.5 mg/mL.

Tanezumab 5 mg is presented as a sterile solution for subcutaneous administration, in a glass pre-filled syringe (PFS). Each PFS contains a sufficient amount of tanezumab to provide the intended dose of drug at a concentration of 5 mg/mL.

Each prefilled syringe is packed in an individual carton. Each prefilled syringe has a unique container number.

##### 5.4.1.2. Placebo for Tanezumab

Placebo for tanezumab is presented as a sterile solution for subcutaneous administration, in a matching glass pre-filled syringe (PFS). Each pre-filled syringe is packaged in an individual carton. Each prefilled syringe has a unique container number.

##### 5.4.1.3. Non-steroidal Anti-inflammatory Drugs (NSAID)

###### 5.4.1.3.1. Celecoxib 100 mg

Celecoxib will be provided as oral capsules containing 100 mg of active celecoxib. Celecoxib 100 mg will be packaged in high-density polyethylene (HDPE) bottles with child resistant closures. The bottles used for the screening period contain 80 capsules (open-label

supply) and the bottles used for the treatment period contain 70 capsules (double-blind supply).

#### **5.4.1.3.2. Placebo to match celecoxib 100 mg**

Placebo for celecoxib will be provided as oral capsules matching those used for celecoxib 100 mg capsules. Placebo to match celecoxib 100 mg will be packaged in HDPE bottles with child resistant closures containing 70 capsules (double-blind supply).

#### **5.4.1.3.3. Naproxen 500 mg**

Naproxen will be provided as oral tablets containing 500 mg of active naproxen. Naproxen 500 mg will be packaged in HDPE bottles with child resistant closures. The bottles used for the screening period contain 80 tablets (open-label supply) and the bottles used for the treatment period contain 70 tablets (double-blind supply).

#### **5.4.1.3.4. Placebo to match naproxen 500 mg**

Placebo for naproxen will be provided as oral tablets matching those used for naproxen 500 mg tablets. Placebo to match naproxen 500 mg will be packaged in HDPE bottles with child resistant closures containing 70 tablets (double-blind supply).

#### **5.4.1.3.5. Diclofenac 75 mg ER**

Diclofenac will be provided as oral extended release capsules containing 75 mg of active diclofenac sodium. Diclofenac 75 mg ER will be packaged in HDPE bottles with child resistant closures. The bottles used for the screening period contain 80 capsules (open-label supply) and the bottles used for the treatment period contain 70 capsules (double-blind supply).

If required due to availability of drug product, a product supplied as diclofenac **SR** 75 mg may be used in place of diclofenac **ER** 75 mg.

#### **5.4.1.3.6. Placebo to match diclofenac 75 mg ER**

Placebo to match diclofenac will be provided as oral capsules matching those used for diclofenac 75 mg ER active. Placebo to match diclofenac 75 mg ER will be packaged in HDPE bottles with child resistant closures containing 70 capsules (double-blind supply).

#### **5.4.1.3.7. Acetaminophen/Paracetamol (rescue medication)**

Acetaminophen/paracetamol will be issued by the study sites in its approved marketed product dress, (carton, bottle, documents). Any approved commercial product of acetaminophen/paracetamol tablet/caplet/capsule is permitted.

### **5.4.2. Preparation and Dispensing**

See the DAI for instructions on how to prepare tanezumab 2.5 mg SC, 5 mg SC and placebo SC for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse,



Storage conditions stated in the single reference safety document (SRSD) (ie, investigator's brochure [IB]; core data sheets [CDS]; US Package Insert or UK Summary of Product Characteristics), will be superseded by the storage conditions stated in the investigational product labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labelling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

## **5.7. Investigational Product Accountability**

The Investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies.

### **5.7.1. Destruction of Investigational Product Supplies**

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If Pfizer authorizes destruction to take place at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

## **5.8. Concomitant Treatment(s)**

### **5.8.1. Prohibited Medications**

Use of analgesics (including marijuana) except acetaminophen/paracetamol is prohibited through Week 64 of the study beginning 48 hours prior to the start of the IPAP (the seven days prior to Randomization/Baseline (Day 1) or at the period of time prior to the start of the IPAP that is at least 5 times the half-life of the particular analgesic used, whichever is greater. Refer to [Appendix 3: Half-Lives of Prohibited Prior and Concomitant Medications](#),

for a detailed washout schedule for prohibited medications. This list is not all-inclusive, the assigned study monitor or study clinician should be consulted for assistance if needed, in determining whether or not specific medications are permitted. Sites must consult product labeling and conduct a taper according to the product instructions if a taper is required.

As specified in [Section 5.8.2](#), occasional use of medication to relieve pain is permitted in certain situations. Use of NSAIDs and COX-2 selective inhibitors (outside of oral investigational product), both prescription or over-the-counter (OTC) is prohibited through the Week 64 visit.

Using IRT, subjects will record the number of days of concomitant NSAID use weekly from Baseline (Day 1) through the Week 80 visit. Additional information regarding NSAID use such as medication names and dosage will be collected by the site on a CRF. Subjects who report concomitant use of prescription or OTC NSAIDs during the study will be managed as per the following guidelines:

- Subjects who report concomitant use of NSAID should be interviewed by study site personnel to determine reason for use and if the subject anticipates being able to comply with concomitant medication restrictions in the future. Subjects who indicate they are taking NSAIDs because of insufficient osteoarthritis pain relief or who indicate that they cannot or will not be able to comply with concomitant medication restrictions will be withdrawn from investigational product and entered in the Early Termination Follow-Up period (refer to [Section 6.4](#)).
- Subjects who reported greater than 10 days (aggregate total) of concomitant NSAID use (any dosage of NSAIDs, for conditions other than OA) in a SC dosing interval (defined as the period of 8 weeks between 2 SC doses) and who after counseling report further concomitant NSAID use should be withdrawn from investigational product and entered in the Early Termination Follow-Up period (refer to [Section 6.4](#)).

Subjects will be instructed that many over-the-counter medications contain NSAIDs and to be aware of this during their selection of OTC medications.

Herbal, homeopathic, and naturopathic remedies should not be initiated during the study; however, subjects who have taken a stable dose of these products for at least 30 days prior to the IPAP will be allowed to continue their regimen. Subjects should be advised that St. John's Wort and other inducers of the cytochrome (CYP3A4/5) enzyme system (eg, carbamazepine and rifampin) may interfere with the efficacy of hormonal contraceptive products.

Biologics (for example: TNF- $\alpha$  inhibitors such as adalimumab, etanercept, infliximab) other than investigational product, and live attenuated vaccines must not have been taken within 3 months prior to the IPAP and are prohibited during the study. Flumist<sup>®</sup> Influenza Virus Vaccine Live, Intranasal or other inhaled influenza vaccines (in regions where these vaccines are approved) are the only exception of a live attenuated vaccine that will be permitted during the study.

### 5.8.2. Permitted Medications

Daily low dose aspirin ( $\leq 325$  mg or per local prescribing practice) therapy for cardiovascular prophylaxis is permitted without restriction.

Medications for other (non-osteoarthritis, non-pain) conditions are permitted provided the subject has received a stable dose for at least 30 days before the IPAP (30 days prior to Screening for antihypertensive medications) and the dose is not expected to change during the study. Note however that dose adjustments (includes starting a new therapy) during the study can be made if required, and recorded on the concomitant medication CRF.

Occasional use of pain medications for pain is permitted in situations such as outpatient diagnostic procedures (eg, colonoscopy, dental procedures) or limited accidental injury (eg, ankle sprains, minor fractures, minor burns/sunburns). Subjects should be counseled to avoid scheduling prospective procedures such that pain medications would be needed within 48 hours of a study visit. Contact the assigned study monitor or study clinician for guidance/approval regarding the use of prohibited medications for other self-limiting conditions, accidental injury or other surgical procedures as the extent of the condition, injury or procedure and the resulting pain medication usage may require termination from the study.

For subjects who have discontinued investigational product, the investigator may prescribe standard of care treatment for subjects to take while completing the 24-week Safety Follow-up period once the last efficacy assessments have been obtained at the visit occurring 16 weeks after the last dose of SC investigational product. In this study, standard of care treatment refers to analgesics approved by FDA (for US subjects) or another applicable Health Authority (for non-US subjects) to relieve the pain of osteoarthritis. These medications include opioids, topical analgesics, NSAIDs, capsaicin products, injectable corticosteroids and viscosupplementation (eg, hyaluronan) and are prescribed at the discretion of the Investigator. Pre-specified analgesics are not considered investigational product but will be reimbursed by Pfizer, if allowed per local regulation while the subject is participating in the 24-week Safety Follow-up period after at least 16 weeks have elapsed since their last dose of SC treatment was administered. Their use will be recorded on the concomitant medication CRF.

### 5.9. Rescue Therapy

Acetaminophen/paracetamol will be issued to the subject by the study sites in its approved marketed product dress, (carton, bottle, documents) for use as rescue medication.

During the Washout period and the Initial Pain Assessment Period, subjects may take rescue medication (acetaminophen/paracetamol) as needed for osteoarthritis or other types of pain or illness up to a maximum daily dose of 3000 mg/day. Rescue medication must be discontinued at least 24 hours prior to the Baseline (Day 1) visit.

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In the event of inadequate pain relief for osteoarthritis during the Double-blind Treatment period (between the Baseline [Day 1] visit and Week 16), subjects may take up to a maximum permitted daily dose of 3000 mg but only up to 3 days per week.

From the Baseline (Day 1) visit through Week 16 visit, subjects taking rescue medication greater than 3 days per week (any level of acetaminophen/paracetamol used specifically for osteoarthritis pain) must be interviewed by study site personnel to determine if this is due to lack of efficacy or other reasons, and the discussion should be noted in the subject's source documents. Subjects who have taken rescue medication more frequently than specified in the protocol during the treatment period due to lack of efficacy and indicate that they cannot or will not follow the rescue medication protocol requirements because of insufficient osteoarthritis pain relief should be withdrawn from investigational product due to lack of efficacy and entered in the Early Termination Follow-up period (refer to [Section 6.4](#)). Subjects who indicate that they anticipate being able to take rescue medication no more than 3 days per week going forward will be allowed to continue in the treatment period. However, if these subjects continue to take rescue medication more than 3 days per week, they should be withdrawn from investigational product and entered into the Early Termination Follow-up period (refer to [Section 6.4](#)).

Between the Week 16 and Week 64 visits, subjects may take acetaminophen / paracetamol rescue medication daily, up to the maximum permitted dose of 3000 mg per day. After the Week 64 visit, subjects may be started on standard of care treatments for osteoarthritis pain. Subjects may continue to use acetaminophen as needed up to the maximal permitted dose of acetaminophen per day as permitted by local or national labeling.

During the Early Termination Follow-up period (described in [Section 6.4](#)); up to 16 weeks after the last dose of SC investigational product, subjects may take acetaminophen/paracetamol rescue medication up to the maximum permitted dose of 3000 mg/day. After Early Termination Visit 2 (approximately 16 weeks after the last dose of SC investigational product) subjects may be started on standard of care treatments for osteoarthritis pain. Subjects may continue to use acetaminophen/paracetamol as needed up to the maximal permitted dose of acetaminophen/paracetamol per day per local or national labeling.

All rescue medication must be discontinued at least 24 hours prior to any scheduled study visit at which efficacy data is collected (ie, up to the Week 64 visit that occurs 16 weeks after the last dose of SC investigational product).

Subjects should bring back rescue medication bottles at each study visit for assessment of compliance.

Subjects will be instructed that many over-the-counter medications contain acetaminophen/paracetamol, and to guard against overuse. Subjects will be instructed to record their acetaminophen / paracetamol rescue medication usage daily via IRT through Week 16. After Week 16 and through the Week 80 visit, usage of acetaminophen/paracetamol rescue medication will be recorded once weekly via the IRT.

The dose and reason for acetaminophen/paracetamol use in instances other than as rescue medication (eg, toothache, headache, fever) must be recorded on the appropriate concomitant medication CRF.

## 6. STUDY PROCEDURES

If possible, each subject's clinic visit should be conducted at approximately the same time of day throughout their participation in the study. As a general rule, scales/instruments should be completed by the subject first, upon arrival at the clinic; vital signs should be assessed prior to blood draws.

Study visit windows are  $\pm 3$  days for Weeks 2 and 4, and  $\pm 7$  days for Weeks 8, 16, 24, 32, 40, 48, 56, 64 and 80. The study visit windows for the telephone visits at Weeks 12, 20, 28, 36, 44, 52, 60, 68, 72, 76 and during the Early Termination Follow-up are  $\pm 7$  days. Study visits should be scheduled with reference to the original baseline visit date as much as possible. Subject scheduling issues should be brought to the attention of the assigned study monitor or study clinician for resolution. Dosing visits should occur no earlier than 7 weeks from the previous injection. The Week 24 X-rays may be obtained up to 30 days before the Week 24 visit, but must be completed and read by the Central Reader before the Week 24 dose of SC investigational product is administered. The visit window for the Week 56 X-rays is  $\pm 30$  days from the nominal time point of the visit. The window for the Week 80 X-rays is  $\pm 30$  days of the nominal time of the visit but should be obtained as close as possible to the Week 80 visit, and preferably no more than 14 days after the Week 80 visit.

Subjects will be reminded to abstain from taking rescue medication 24 hours prior any study visit at which efficacy data is collected.

### 6.1. Screening Period

The Screening period will consist of a maximum of 37 days prior to Randomization and will last a minimum of 2 or 3 weeks (14 or 21 days). The 2 or 3-week minimum Screening period is needed to complete the pre-randomization, NSAID regimen stabilization. The length of the NSAID regimen stabilization period will depend on the NSAID subjects are receiving in the 30 days prior to screening. The NSAID regimen stabilization period will be a minimum of 2 weeks if the pre-study NSAID is celecoxib, naproxen or diclofenac or a minimum of 3 weeks if the pre-study NSAID is aceclofenac, loxoprofen, ibuprofen, meloxicam, nabumetone, sulindac, or ketoprofen. Prior to entering the Initial Pain Assessment Period (IPAP), subjects taking prohibited medications must complete the required washout from these medications for at least 5 half-lives or 48 hours (whichever is greater). Screening procedures should be staged to minimize burden to the subject and to minimize conduct of procedures that may not be required if a subject is found to be ineligible. To assist in this staging, screening procedures have been sorted into Screening Stage 1 and Screening Stage 2.

Written informed consent will be obtained from each subject prior to any trial assessments. Each subject will be assessed as to his/her suitability per inclusion/exclusion criteria review.

Subject demographics and the date of OA diagnosis for every affected joint will be obtained. A comprehensive medical history and concomitant medication review will be performed for each subject; in addition, a comprehensive evaluation of musculoskeletal history and musculoskeletal physical exam will be performed (refer to [Section 7.3.2](#)). The index joint (hip or knee) will be selected at the Screening Stage 1 visit. If bilateral knee and/or hip pain is present, the investigator will select the more painful joint as the study (index) joint. X-ray confirmation of eligibility (Kellgren-Lawrence grade  $\geq 2$  for selected index joint and absence of exclusionary conditions) will be obtained from the imaging Central Reader based on the radiographs of each knee, hip and shoulder (and any other major joints imaged at Screening) prior to the Screening Stage 2 visit. Anticipate that it may take up to 2 weeks to obtain X-ray confirmation from the Central Reader.

Evidence of subjects receiving a stable dose regimen of oral NSAID therapy at doses and for the duration/frequency specified in protocol inclusion criterion along with a history of insufficient pain relief from, inability to tolerate or contraindication to taking acetaminophen/paracetamol and tramadol or opioid treatments will be clearly documented on the appropriate CRF page. The required level of evidence to establish that subjects meet this inclusion criterion will be based upon the investigator's judgment. Investigators should rely upon available medical records that he or she may already have access to, prescription medication records (eg, retail pharmacy records), records or information provided by referring physicians and/or subject historical recall if the investigator is satisfied with the level of detail subjects are able to provide on past medication use. Investigators should clearly document in source records the information used to establish whether a subject does or does not meet this inclusion criterion. As a guide, investigators should document medication names, medication doses, reasons for use, dates of use and reason for discontinuation. If one or more of the above medications could not be used due to contraindication or if the subject refuses to take the medication due to fear of known side effects, this should also be clearly documented with supporting detail. **NOTE: In Japan, Investigators will also need to document the outcome of a trial of acetaminophen.**

#### 6.1.1. Screening Period Stage 1 (Initial Screening Visit)

- Informed consent.
- Demographics and general medical history.
  - Assessment of depression by medical history (Use of PHQ-9 is optional and suggested as a tool to assess seriousness of depression if needed. If the PHQ-9 is utilized, the completed questionnaire should be archived in the subject's source documents.).
- Numeric Pain Scale rating (IRT) for major joints (bilateral shoulders, hips and knees) and any painful joint imaged at Screening.
- Primary diagnosis and selection of index hip or knee.

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verification prior to Baseline. Refer to [Section 7.3.3](#) for specific instructions related to laboratory screening tests.

- Inclusion/exclusion review (pending results of laboratory tests, ECG and X-rays). If a subject qualifies other than pending results they may begin the washout of prohibited pain medications (refer to [Section 5.8.1](#)). Subjects who are found to be ineligible subsequent to the receipt of disqualifying laboratory, ECG or X-ray results may be asked to return requested study related materials and will exit the Screening period (Screen Failure).
- Female subjects of child-bearing potential will be instructed on the contraception requirements for this study; the investigator or designee will confirm that female subjects of child-bearing potential have selected 2 highly effective forms of contraception from the list of acceptable methods and instruct the subject in their consistent and correct use. The conversation will be documented in the subject chart.
- Dispense Screening period rescue medication; subjects will be instructed on the permissible amounts of rescue medication during the washout period, during the IPAP and during the treatment period, as well as the need to refrain from rescue medication use at least 24 hours prior to a study visit (refer to [Section 5.8.2](#)).
- Subjects in Japan who have not had a trial of acetaminophen (as monotherapy or in combination with tramadol) for their osteoarthritis, will undergo at least 1-week trial of an approved daily dose of acetaminophen after obtaining informed consent because subjects are required to have documentation that acetaminophen has not provided sufficient pain relief. The 1-week trial of acetaminophen should be completed at least two weeks prior to the Baseline/Day 1 visit. If they obtain sufficient response to acetaminophen, as judged by the subject and Investigator, they will then be withdrawn from the study. Those who do not have a sufficient response to acetaminophen will continue with the screening process. Subjects who have not achieved an adequate response to an approved dose of Tramacet<sup>®</sup> (1-2 tablets four times a day (QID): total daily tramadol 150 mg – 300 mg and acetaminophen 1300 mg – 2600 mg) can be considered to meet the acetaminophen and tramadol inclusion criterion.
- Dispense Screening period oral NSAID.

**NOTE:** Beginning at Screening, subjects should use study-supplied oral investigational product (NSAID during Screening and NSAID or matching placebo post-randomization) through Week 56.

Subjects who were receiving celecoxib, diclofenac or naproxen prior to Screening will receive this same oral NSAID but may need to change dosing regimen to a BID dosing regimen for the duration of the study. Subjects must maintain the BID dosing regimen of celecoxib 100 mg, naproxen 500 mg, or diclofenac ER 75 mg for at least

the final 2 weeks of the Screening period directly prior to the Baseline (Randomization/Day 1) Visit.

Subjects who were receiving aceclofenac, loxoprofen, ibuprofen, meloxicam, nabumetone, sulindac or ketoprofen prior to Screening will be assigned to celecoxib, naproxen or diclofenac. The specific NSAID that subjects will be assigned to (celecoxib, naproxen or diclofenac) will be the choice of the investigator. Subjects will use this NSAID for the remainder of the Screening period and will be stabilized on a dosing regimen of celecoxib 100 mg BID, naproxen 500 mg BID, or diclofenac ER 75 mg BID for at least the final 3 weeks of the Screening period directly prior to the Baseline (Randomization/Day 1) visit.

During NSAID regimen stabilization, all subjects will be expected to maintain a minimum compliance of 70% (average of 5 of 7 days per week).

### 6.1.2. Screening Period Stage 2

Subjects who satisfy inclusion/exclusion criteria (to this point) and for whom radiographic eligibility has been confirmed, will undergo the following additional screening procedures:

- MRIs of each hip and knee (all subjects).
- DXA scans of the hip and lumbar spine.

**NOTE:** DXA scans will only be performed for subjects meeting National Osteoporosis Foundation recommendations for bone mineral density testing (refer to [Section 7.3.12](#)).

- Subjects at selected sites will be provided with activity level monitors (accelerometers) and instructions on completion of 7 consecutive days of activity monitoring (refer to [Section 7.3.9](#)).
- Subjects will be instructed in the use of the IRT system to record daily/weekly pain ratings, rescue medication use, with specific instructions as when to test the system and when to begin entering data.
- Subjects will maintain the BID dosing regimen of celecoxib 100 mg, naproxen 500 mg, or diclofenac ER 75 mg for at least the final 2 or 3 weeks (average of 5 of 7 days per week; ie, minimum 70% compliance) of the Screening period directly prior to the Baseline (Day 1) visit.

### 6.1.3. Washout Period

The beginning of the Washout Period will preferably be scheduled based on the planned start of the Initial Pain Assessment Period so as to minimize the time spent without analgesic medications prior to Randomization. The Washout Period will include the discontinuation and washout of all prohibited medications for at least 5 half-lives or 48 hours (whichever is greater) prior to the Initial Pain Assessment Period (the 7 days prior to randomization) and



- Sites performing activity level monitoring (actigraphy) will collect activity level monitors from subjects.
- Inclusion/exclusion review (including results of ECG, laboratory and X-rays obtained at the Screening visits).
- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.

**NOTE:** Subjects should be thoroughly instructed on completion of Patient's Global Assessment of Osteoarthritis questionnaires, no coaching or other interpretative assistance should be given to subjects during completion of these questionnaires.

- Musculoskeletal physical examination.
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Review of concomitant medication.
- Rescue medication (acetaminophen/paracetamol) review.
- Baseline NSAID compliance review.
- Instruction/review of subject compliance with daily/weekly assessments and operation of the IRT.
- Confirm with females of child-bearing potential that they understand and are willing to follow the contraceptive requirements.
- Adverse events that occurred after signing the Informed Consent Document (pretreatment adverse events).
- Urine pregnancy test for females of childbearing potential (must be negative).

#### **6.2.1.2. Randomization**

Subjects satisfying eligibility requirements will be randomized via an IRT system. The randomization number assigned to the subject will be provided by the system. Subjects satisfying eligibility requirements will undergo the following assessments prior to the first dose of investigational product.

### 6.2.1.3. Pre-dosing (Day 1)

Randomized subjects will undergo the following assessments prior to the first dose of investigational product. Some of these may be performed prior to randomization for convenience:

- WPAI:OA.
- EQ-5D-5L.
- Assessment of Health Care Resource Utilization.
- Lower Extremity Activity Scale (LEAS).
- Neurologic exam/Neuropathy Impairment Score.
- Clinical laboratory tests (blood chemistry and hematology).
- Serum samples for 25-hydroxy vitamin D and parathyroid hormone.
- Serum and plasma retention samples.
- Blood sample for anti-tanezumab antibody assessment (refer to [Section 7.3.14](#)).
- Blood samples for PK and PD (NGF) analyses (refer to [Section 7.5](#)).
- Blood and urine samples for biomarkers (fasting if possible, urine sample should be from 2<sup>nd</sup> void of the day or after; refer to [Section 7.6](#)).
- Blood sample for banked biospecimens (see [Section 7.7.1](#) Markers of Drug Response and Additional Research, [Section 7.7.2](#)).
- Dispense rescue medication.
- Dispense oral investigational product (NSAID or matching placebo).
- Females of child-bearing potential to be reminded of contraceptive requirements.

### 6.2.1.4. Dosing (Day 1)

- Subjects will receive a single SC injection of blinded investigational product according to the treatment assigned by the IRT system (refer to [Section 5](#)).

The administration of investigational product must be performed by trained medical staff and where facilities to handle allergic reactions are available (eg, diphenhydramine hydrochloride for injection, epinephrine 1:1000 for management of acute or severe reactions such as anaphylaxis). Should a subject experience symptoms typical of an allergic reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema), then investigational product

administration should be discontinued immediately and permanently. Subjects will receive appropriate treatment such as corticosteroids, antihistamine, or acetaminophen at the discretion of the Investigator. No other dosage modifications are allowed.

- A morning dose of oral investigational product (NSAID or matching placebo) will not be administered on Study Day 1. The evening dose of oral investigational product on Study Day 1 and all subsequent dosing of oral investigational product will be performed by subjects at home.

#### 6.2.1.5. Post-dosing (Day 1)

Subjects will be observed in the clinic for at least 1 hour after dosing. The following procedures will be completed at approximately 1-hour post-dose:

- Review and record adverse events.

Each subject should be reminded to seek medical care and/or contact the Investigator if the subject experiences symptoms of an acute or severe hypersensitivity reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema) after leaving the clinic.

#### 6.2.2. Week 2 Clinic Visit

The following procedures will be performed:

- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Musculoskeletal physical examination.
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required, refer to [Section 7.3.13](#)).
- Concomitant medication review/update.
- Adverse event review.
- Subject daily/weekly IRT entry compliance and data review (daily index joint pain score, weekly non-index joint pain assessment and as applicable, daily rescue medication and weekly NSAID use entries).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.

- Review daily and weekly (as applicable) joint pain scores.
- Rescue medication (acetaminophen/paracetamol) compliance review/dispense.
- Oral investigational product (NSAID or matching placebo) compliance review.
- Females of child-bearing potential to be reminded of contraceptive requirements.
- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect synovial fluid, plasma and serum samples for analysis (refer to [Sections 7.5.1](#), [7.5.2](#), and [7.5.3](#)).

### 6.2.3. Week 4 Clinic Visit

- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.
- Vital signs after sitting for at least 5 minutes, (blood pressure and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Musculoskeletal physical examination.
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required).
- Lower Extremity Activity Scale (LEAS).
- Concomitant medication review/update.
- Adverse event review.
- Subject daily/weekly IRT entry compliance (daily index joint pain score, weekly non-index joint pain assessment and as applicable, daily rescue medication and weekly NSAID use entries).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review daily and weekly (as applicable) joint pain scores.
- Rescue medication (acetaminophen/paracetamol) compliance review/dispense.
- Oral investigational product (NSAID or matching placebo) compliance review.
- Females of child-bearing potential to be reminded of contraceptive requirements;

- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect synovial fluid, plasma and serum samples (refer to [Sections 7.5.1](#), [7.5.2](#) and [7.5.3](#)).

#### **6.2.4. Week 8 Clinic Visit**

##### **6.2.4.1. Pre-dosing**

- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.
- EQ-5D-5L.
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Musculoskeletal physical examination.
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required).
- Lower Extremity Activity Scale (LEAS).
- Concomitant medication review/update.
- Adverse event review.
- Subject daily/weekly IRT entry compliance (daily index joint pain score, weekly non-index joint pain assessment and as applicable, daily rescue medication and weekly NSAID use entries).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review daily and weekly (as applicable) joint pain scores.
- Rescue medication (acetaminophen/paracetamol) compliance review/dispense.
- Oral investigational product (NSAID or matching placebo) compliance review/dispense.
- Blood samples for PK and PD (NGF) analyses (refer to [Section 7.5](#)).
- Blood sample for anti-tanezumab antibody assessment (refer to [Section 7.3.14](#)).

- Blood and urine samples for biomarkers (fasting if possible, urine sample should be from 2<sup>nd</sup> void of the day or after; refer to [Section 7.6](#)).
- Urine pregnancy test for females of childbearing potential (must be negative prior to dosing).
- Females of child-bearing potential to be reminded of contraceptive requirements.
- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect a synovial fluid sample (refer to [Section 7.5.3](#)).

#### **6.2.4.2. Subcutaneous Dosing**

Subjects will receive a single injection of blinded, SC investigational product according to the treatment assigned by the IRT system (refer to [Section 5](#)).

#### **6.2.4.3. Post-dosing**

Subjects will be observed in clinic for at least 1 hour after dosing. The following procedures will be completed at approximately 1-hour post-dose:

- Review and record adverse events.
- Sites that are performing actigraphy will provide subjects who completed Baseline activity monitoring (actigraphy) with instructions and an actigraphy device to be used over the course of 14 consecutive days between Week 14 and the Week 16 Visit (refer to [Section 7.3.9](#)).

Each subject should be reminded to seek medical care and/or contact the Investigator if the subject experiences symptoms of an acute or severe hypersensitivity reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema) after leaving the clinic.

#### **6.2.5. Week 12 Telephone Contact**

- Review/update of concomitant medication and subject daily/weekly IRT entries compliance (daily index joint pain score, weekly non-index joint pain assessment and as applicable, daily rescue medication and weekly NSAID use entries).
- Compliance with oral investigational product (NSAID or matching placebo).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review daily and weekly (as applicable) joint pain scores.
- Rescue medication (acetaminophen / paracetamol) compliance review.

- Adverse events review.
- Females of child-bearing potential to be reminded of contraceptive requirements.
- Sites that are performing actigraphy should remind their subjects to conduct 14 consecutive days of actigraphy between Week 14 and the Week 16 visit.

## 6.2.6. Week 16 Clinic Visit (Primary Efficacy Time Point)

### 6.2.6.1. Pre-dosing

- Review subject eligibility.

**NOTE:** At the Week 16 visit, subjects must have a 30% or greater reduction in WOMAC Pain subscale relative to Baseline in the index joint and a 15% or greater reduction in WOMAC Pain subscale from Baseline at either Week 2, 4 or 8 in order to continue investigational product. As a risk mitigation measure, subjects who do not meet this efficacy response criteria will be discontinued from the Double-blind Treatment period and enter the 24-week Early Termination Follow-up period (refer to [Section 6.4](#)). The efficacy response calculation will be performed by the IRT system.

- Adverse event review.
- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.
- WPAI:OA.
- EQ-5D-5L.
- TSQM (v.II).
- mPRTI.
- Lower Extremity Activity Scale (LEAS).
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Musculoskeletal physical examination.
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required).
- Serum and plasma retention samples.

- Clinical laboratory tests (blood chemistry and hematology).
- Blood sample for PK analysis (refer to [Section 7.5](#)).
- Blood sample for anti-tanezumab antibody assessment (refer to [Section 7.3.14](#)).
- Blood and urine samples for biomarkers (fasting if possible, urine sample should be from 2<sup>nd</sup> void of the day or after; refer to [Section 7.6](#)).
- Urine pregnancy test for females of childbearing potential (must be negative prior to dosing).
- Sites performing activity level monitoring (actigraphy) will collect activity level monitors from subjects.
- Concomitant medication review/update.
- Subject daily/weekly IRT entry compliance (daily index joint pain score, weekly non-index joint pain assessment and as applicable, daily rescue medication and weekly NSAID use entries).
- Instruct subjects that after the Week 16 visit the index joint pain score, non-index joint pain assessment, rescue medication and NSAID use will all be assessed once weekly using IRT (See [Section 7.1](#)).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review daily and weekly (as applicable) joint pain scores.
- Rescue medication (acetaminophen/paracetamol) compliance review/dispense.
- Oral investigational product (NSAID or matching placebo) compliance review/dispense.
- Females of child-bearing potential to be reminded of contraceptive requirements.
- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect synovial fluid and serum samples (refer to [Sections 7.5.2, 7.5.3](#)).

#### 6.2.6.2. Subcutaneous Dosing

Eligible subjects will receive a single injection of blinded SC investigational product according to the treatment assigned by the IRT system (refer to [Section 5](#)).

### 6.2.6.3. Post-dosing

Subjects will be observed in clinic for at least 1 hour after dosing. The following procedures will be completed at approximately 1-hour post-dose:

- Review and record adverse events.
- Schedule subjects for follow-up radiographic assessments (X-rays) of each shoulder, hip and knee and any other major joint for which a radiograph was obtained at the Screening visit or any at risk joint identified during the study period (refer to [Section 7.3.10](#)).
- Subjects meeting criteria (subjects who had Kellgren-Lawrence grade 3 or 4 osteoarthritis of any knee or hip at Screening/Baseline, refer to [Section 7.3.11](#)) should be scheduled for follow-up MRIs of each hip and knee.

**NOTE:** Follow-up radiographs and MRIs (if applicable) should be scheduled to occur at least 2 weeks and no more than 4 weeks (30 days) prior to the Week 24 clinic visit.

Each subject should be reminded to seek medical care and/or contact the Investigator if the subject experiences symptoms of an acute or severe hypersensitivity reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema) after leaving the clinic.

### 6.2.7. Week 20 Telephone Contact

- Review/update of concomitant medication and subject weekly IRT entries compliance (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Compliance with oral investigational product (NSAID or matching placebo).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review weekly joint pain scores.
- Rescue medication (acetaminophen / paracetamol) compliance review.
- Adverse events review.
- Females of child-bearing potential to be reminded of contraceptive requirements.
- Verify that follow-up radiographs and MRIs (if applicable) required for Week 24 visit have been scheduled and will be completed (refer to [Sections 7.3.10](#) and [7.3.11](#)).

**NOTE:** Follow-up radiographs and MRIs (if applicable) should be completed at least 2 weeks prior to the Week 24 clinic visit. Local radiology reports should be obtained.



- Oral investigational product (NSAID or matching placebo) compliance review/dispense.
- Urine pregnancy test for females of childbearing potential (must be negative prior to dosing).
- Females of child-bearing potential to be reminded of contraceptive requirements.
- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect synovial fluid, plasma and serum samples (refer to [Sections 7.5.1](#), [7.5.2](#) and [7.5.3](#)).

#### **6.2.8.2. Subcutaneous Dosing**

Eligible subjects will receive a single injection of blinded SC investigational product according to the treatment assigned by the IRT system (refer to [Section 5](#)).

#### **6.2.8.3. Post-dosing**

Subjects will be observed in clinic for at least 1 hour after dosing. The following procedures will be completed at approximately 1-hour post-dose:

- Review and record adverse events.

Each subject should be reminded to seek medical care and/or contact the Investigator if the subject experiences symptoms of an acute or severe hypersensitivity reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema) after leaving the clinic.

#### **6.2.9. Week 28 Telephone Contact**

- Review/update of concomitant medication and subject weekly IRT entries compliance (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Compliance with oral investigational product (NSAID or matching placebo).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review weekly joint pain scores.
- Rescue medication (acetaminophen/paracetamol) compliance review.
- Adverse events review.
- Females of child-bearing potential to be reminded of contraceptive requirements.

## 6.2.10. Week 32 Clinic Visit

### 6.2.10.1. Pre-dosing

- Adverse event review.
- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Musculoskeletal physical examination.
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required).
- Concomitant medication review/update.
- Subject weekly IRT entry compliance review (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review weekly joint pain scores.
- Rescue medication (acetaminophen/paracetamol) compliance review/dispense.
- Oral investigational product (NSAID or matching placebo) compliance review/dispense.
- Blood samples for PK analyses (refer to [Section 7.5](#)).
- Blood sample for anti-tanezumab antibody assessment (refer to [Section 7.3.14](#)).
- For subjects that performed activity level monitoring via accelerometry, blood and urine samples for biomarkers (fasting if possible, urine sample should be from 2<sup>nd</sup> void of the day or after; refer to [Section 7.6](#)).
- Urine pregnancy test for females of childbearing potential (must be negative prior to dosing).
- Females of child-bearing potential to be reminded of contraceptive requirements.

- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect synovial fluid and serum samples (refer to [Sections 7.5.2, 7.5.3](#)).

#### **6.2.10.2. Subcutaneous Dosing**

Eligible subjects will receive a single injection of blinded, SC investigational product according to the treatment assigned by the IRT system (refer to [Section 5](#)).

#### **6.2.10.3. Post-dosing**

Subjects will be observed in clinic for at least 1 hour after dosing. The following procedures will be completed at approximately 1-hour post-dose:

- Review and record adverse events.

Each subject should be reminded to seek medical care and/or contact the Investigator if the subject experiences symptoms of an acute or severe hypersensitivity reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema) after leaving the clinic.

#### **6.2.11. Week 36 Telephone Contact**

- Review/update of concomitant medication and subject weekly IRT entries compliance (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Compliance with oral investigational product (NSAID or matching placebo).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review weekly joint pain scores.
- Rescue medication (acetaminophen/paracetamol) compliance review.
- Adverse events review.
- Females of child-bearing potential to be reminded of contraceptive requirements.

#### **6.2.12. Week 40 Clinic Visit**

##### **6.2.12.1. Pre-dosing**

- Adverse event review.
- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.
- EQ-5D-5L.



Each subject should be reminded to seek medical care and/or contact the Investigator if the subject experiences symptoms of an acute or severe hypersensitivity reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema) after leaving the clinic.

#### **6.2.13. Week 44 Telephone Contact**

- Review/update of concomitant medication and subject weekly IRT entries compliance (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Compliance with oral investigational product (NSAID or matching placebo).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review weekly joint pain scores.
- Rescue medication (acetaminophen/paracetamol) compliance review.
- Adverse events review.
- Females of child-bearing potential to be reminded of contraceptive requirements.

#### **6.2.14. Week 48 Clinic Visit**

##### **6.2.14.1. Pre-dosing**

- Adverse event review.
- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Musculoskeletal physical examination.
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required).
- Concomitant medication review/update.
- Subject weekly IRT entries compliance review (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).



### 6.2.15. Week 52 Telephone Contact

- Review/update of concomitant medication and subject weekly IRT entries compliance (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Compliance with oral investigational product (NSAID or matching placebo).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review weekly joint pain scores.
- Rescue medication (acetaminophen/paracetamol) compliance review.
- Adverse events review.
- Females of child-bearing potential to be reminded of contraceptive requirements.
- Schedule subject for follow-up radiographic assessments (X-rays) of each shoulder, hip and knee and any other major joint for which a radiograph was obtained at the Screening visit or any at risk joint identified during the study period (refer to [Section 7.3.10](#)).
- Sites that are performing actigraphy should remind their subjects to conduct 14 consecutive days of actigraphy between Week 54 and the Week 56 visit.
- Subjects meeting criteria (subjects who had Kellgren-Lawrence Grade 3 or 4 osteoarthritis of any knee or hip at Screening/Baseline, refer to [Section 7.3.11](#)) should be scheduled for magnetic resonance imaging of the each hip and knee.

**NOTE:** Follow-up radiographs and MRIs should be completed within 30 days (ie, between Weeks 52 and 60) of the Week 56 visit. Local radiology reports should be obtained.

### 6.2.16. Week 56 Clinic Visit (End of Double-Blind Treatment)

- Adverse event review.
- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.
- WPAI:OA.
- EQ-5D-5L.
- TSQM (v.II).

- mPRTI.
- Lower Extremity Activity Scale (LEAS).
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Serum and plasma retention samples.
- ECG (12-lead).
- Body weight.
- Musculoskeletal physical examination.
- Survey of Autonomic Symptoms (SAS).
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required).
- Sites performing activity level monitoring (actigraphy) will collect activity level monitors from subjects.
- General physical examination.
- Concomitant medication review/update.
- Subject weekly IRT entries compliance review (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review weekly joint pain scores.
- Rescue medication (acetaminophen/paracetamol) compliance review/dispense.
- Oral investigational product (NSAID or matching placebo) compliance review.
- Blood sample for anti-tanezumab antibody assessment (refer to [Section 7.3.14](#)).
- Blood samples for PK and PD (NGF) analyses (refer to [Section 7.5](#)).

- For subjects that performed activity level monitoring via accelerometry, blood and urine samples for biomarkers (fasting if possible, urine sample should be from 2<sup>nd</sup> void of the day or after; refer to [Section 7.6](#)).
- Serum pregnancy test for females of childbearing potential.
- Females of child-bearing potential to be reminded of contraceptive requirements.
- If not already completed, schedule subject for follow-up radiographic assessments (X-rays) of each shoulder, hip and knee and any other major joint for which a radiograph was obtained at the Screening visit or any at risk joint identified during the study period (refer to [Section 7.3.10](#)).
- If not already completed, subjects meeting criteria (subjects who had Kellgren-Lawrence Grade 3 or 4 osteoarthritis of any knee or hip at Screening/Baseline, refer to [Section 7.3.11](#)) should be scheduled for magnetic resonance imaging of each hip and knee.

**NOTE:** Follow-up radiographs and MRIs should be completed within 30 days of the Week 56 visit (ie, no later than the Week 60 telephone contact). Local radiology reports should be obtained.

- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect a synovial fluid sample (refer to [Section 7.5.3](#)).

### 6.3. Safety Follow-up Period

The Safety Follow-up period begins once the Week 56 procedures have been completed and concludes with completion of the Week 80 visit procedures. The Safety Follow-up period is 24 weeks in duration and consists of 2 clinic visits (Weeks 64 and 80) and 4 telephone contacts (Weeks 60, 68, 72 and 76) between site staff and enrolled subjects.

#### 6.3.1. Week 60 Telephone Contact

- Review/update of concomitant medication and subject weekly IRT entries compliance (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Monitor for violations of concomitant NSAID (outside of oral investigational product) use.
- Review weekly joint pain scores.
- Rescue medication (acetaminophen / paracetamol) compliance review.
- Adverse events review.

- Confirm that follow-up radiographs and MRIs if required (refer to [Section 7.3.10, 7.3.11](#)) have been completed, local radiology reports should be obtained.
- Females of child-bearing potential to be reminded of contraceptive requirements.

### 6.3.2. Week 64 Clinic Visit

- Adverse event review.
- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.
- WPAI:OA.
- EQ-5D-5L.
- Health Care Resource Utilization.
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Clinical laboratory tests (blood chemistry, hematology, serum 25-hydroxy vitamin D and parathyroid hormone).
- Serum and plasma retention samples.
- Serum pregnancy test for females of childbearing potential.
- Musculoskeletal physical examination.
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required).
- Concomitant medication review/update.
- Subject weekly IRT entries compliance review (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Monitor for violations of concomitant NSAID use.
- Review weekly joint pain scores.
- Rescue medication (acetaminophen/paracetamol) compliance review/dispense.

- Blood sample for anti-tanezumab antibody assessment (refer to [Section 7.3.14](#)).
- Blood samples for PK and PD (NGF) analyses (refer to [Section 7.5](#)).
- For subjects that performed activity level monitoring via accelerometry, blood and urine samples for biomarkers (fasting if possible, urine sample should be from 2<sup>nd</sup> void of the day or after; refer to [Section 7.6](#)).
- Initiate standard of care treatment for osteoarthritis pain at the discretion of the investigator.
- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect a synovial fluid sample (refer to [Section 7.5.3](#)).

### **6.3.3. Week 68 Telephone Contact**

- Review/update of concomitant medication and subject weekly IRT entries compliance (weekly index joint pain score, weekly non-index joint pain assessment as applicable, weekly rescue medication and weekly NSAID use entries).
- Adverse Events review.

### **6.3.4. Week 72 Telephone Contact**

- Review/update of concomitant medication and subject weekly IRT entries compliance (weekly index joint pain score, weekly non-index joint pain assessment as applicable, weekly rescue medication and weekly NSAID use entries).
- Adverse Events review.

### **6.3.5. Week 76 Telephone Contact**

- Review/update of concomitant medication and subject weekly IRT entries compliance (weekly index joint pain score, weekly non-index joint pain assessment as applicable, weekly rescue medication and weekly NSAID use entries).
- Adverse Events review.
- Schedule subject for follow-up radiographic assessments (X-rays) of each shoulder, hip and knee and any other major joint for which a radiograph was obtained at the Screening visit or any at risk joint identified during the study period (refer to [Section 7.3.10](#)).
- Subjects meeting criteria (subjects who had Kellgren-Lawrence Grade 3 or 4 osteoarthritis of any knee or hip at Screening/Baseline, refer to [Section 7.3.11](#)) should be scheduled for magnetic resonance imaging of each hip and knee.

**NOTE:** Follow-up radiographs and MRIs should be completed up to 30 days before and preferably, no more than 14 days after the Week 80 visit and local radiology reports should be obtained.

### 6.3.6. Week 80 Clinic Visit (End of Study)

- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- ECG (12-lead).
- Musculoskeletal physical examination.
- Survey of Autonomic Symptoms (SAS).
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required).
- Lower Extremity Activity Scale (LEAS).
- Health Care Resource Utilization.
- Concomitant medication review/update.
- Review weekly index joint pain scores and weekly non-index joint pain assessment as applicable, weekly rescue medication and weekly NSAID use entries.
- Adverse event review.
- Blood sample for anti-tanezumab antibody assessment (refer to [Section 7.3.14](#)).
- For subjects that performed activity level monitoring via accelerometry, blood and urine samples for biomarkers (fasting if possible, urine sample should be from 2<sup>nd</sup> void of the day or after; refer to [Section 7.6](#)).
- If not already completed, schedule subject for follow-up radiographic assessments (X-rays) of each shoulder, hip and knee and any other major joint for which a radiograph was obtained at the Screening visit or any at risk joint identified during the study period (refer to [Section 7.3.10](#)).
- If not already completed, subjects meeting criteria (subjects who had Kellgren-Lawrence Grade 3 or 4 osteoarthritis of any knee or hip at Screening/Baseline, refer to [Section 7.3.11](#)) should be scheduled for magnetic resonance imaging of each hip and knee.

**NOTE:** Follow-up radiographs and MRI scans should be completed up to 30 days before and preferably, no more than 14 days after the Week 80 visit and local radiology reports should be obtained.

- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect synovial fluid, plasma and serum samples (refer to [Sections 7.5.1](#), [7.5.2](#) and [7.5.3](#)).

#### **6.4. Subject Withdrawal/Early Termination**

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. A subject thought to be lost to follow-up, must be contacted through a minimum of 3 documented phone call attempts and, if phone calls are unsuccessful, a certified letter sent to the subject. In any circumstance, every effort should be made to document the subject's outcome, if possible. The Investigator should inquire about the reason for withdrawal, request the return of all unused investigational product, follow-up with the subject regarding any unresolved adverse events and request that the subject return for follow-up visits as indicated in the schedule below. Females of child-bearing potential should be reminded to continue contraceptive measures at least 112 days (16 weeks) after the last dose of SC investigational product.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. Pfizer may retain and continue to use any data collected before such withdrawal of consent.

Subjects discontinuing from treatment (prior to Week 56), whether at their request or at the decision of the investigator, will be required to undergo 24 weeks of post-treatment follow-up (as described in [Section 6.4.1](#)). The 24 weeks of follow-up will be obtained through 3 clinic visits and monthly phone calls to yield 24 weeks of follow-up, as described in [Section 6.4.1](#). Subjects will be asked to continue to enter pain scores for index and non-index joints (as applicable) via IRT, weekly, through the end of the 24 week safety follow-up period. On a weekly basis during the 24 week safety follow-up period, subjects will also be asked to continue to record rescue medication and NSAID use.

Radiographs of each knee, shoulder and hip (and any other major joint imaged at Screening or identified as at risk during the study) should be performed as soon as possible after the decision to withdraw from the study has been made, provided at least 30 days have passed since the last set of X-rays were collected. Subjects meeting criteria (subjects who had Kellgren-Lawrence Grade 3 or 4 osteoarthritis of any knee or hip at Screening/Baseline, refer to [Section 7.3.11](#)) should also be scheduled for magnetic resonance imaging of each hip and knee. The remainder of efficacy and safety assessments should be done at the scheduled first

visit which is to occur approximately 8 weeks after the last dose of SC investigational product (refer to [Section 6.4.1.1](#)).

The site should also schedule the subject for two additional clinic visits. The second visit should be scheduled to occur approximately 16 weeks after the subject's last dose of SC investigational product (which corresponds to more than 5 times the elimination half-life of tanezumab) to collect safety and efficacy data (refer to [Section 6.4.1.3](#)). Once the clinic visit 16 weeks after the last administration of SC investigational product has been completed and final efficacy assessments have been collected, standard of care treatment may be offered to subjects for the remaining 8 weeks of the required follow-up period. The third and final clinic visit should be scheduled to take place approximately 24 weeks after the subject received the last dose of SC investigational product (refer to [Section 6.4.1.5](#)). That visit includes repeat X-rays of the hips, knees and shoulders as well as any additional joint that was imaged at Screening or any joint identified as at risk during the study, providing at least 30 days have elapsed since the last radiographs were obtained. Subjects meeting criteria (subjects who had Kellgren-Lawrence Grade 3 or 4 osteoarthritis of any knee or hip at Screening/Baseline, refer to [Section 7.3.11](#)) should also be scheduled for magnetic resonance imaging of each hip and knee. Follow-up radiographs and MRIs should be completed up to 30 days before and preferably, no more than 14 days after the Early Termination Follow-up Visit 3 (24 weeks after last dose of SC investigational product). Telephone contact will be made with subjects at approximately 12 and 20 weeks following the last SC dose of investigational product. Every effort should be made to have the subject agree to complete the entire 24 week Early Termination Safety Follow-up described in [Section 6.4.1](#).

In the event a subject refuses the Early Termination safety follow-up, or chooses to discontinue during the safety follow-up (after Week 56 and through Week 80), a complete early termination visit should be performed. This early termination visit should include all procedures scheduled for the Week 64 and Week 80 visits unless the Week 64 visit has already been completed, in which case only Week 80 procedures will be required. In addition, if the Week 56 visit was not completed prior to termination, a general physical examination, body weight, WPAI:OA, EQ-5D-5L, TSQM v.II and mPRTI will also be obtained. Subjects will be advised to continue their contraception regimen during a period of 112 days (16 weeks) after the last dose of investigational product.

Subjects entered in the Early Termination Follow-up period will be able to take acetaminophen/paracetamol rescue medication daily up to the Early Termination Follow-up period Visit 2 (which occurs 16 weeks after the last dose of SC investigational product), but will be advised not to exceed the maximal daily dose of 3000 mg. Subjects will be requested not to take acetaminophen/paracetamol (or any other analgesic) in the 24 hours that precede clinic visits at which efficacy assessments are collected (Early Termination Follow-up period Visits 1 and 2, which occur 8 and 16 weeks after the last dose of SC investigational product, respectively). After the second Early Termination Follow-up visit occurring approximately 16 weeks after the last SC dose of investigational product, subjects may be started on standard of care treatments for osteoarthritis pain. Subjects may continue to use acetaminophen/paracetamol as needed per local or national labeling.

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#### **6.4.1. Early Termination Follow-up Period**

As soon as possible following a decision to withdraw a subject from the study is made the following procedures should be completed:

- Provided at least 30 days have passed since the last set of X-rays were collected, schedule subjects for follow-up radiographic assessments (X-rays) of each shoulder, hip and knee and any other major joint for which a radiograph was obtained at the Screening visit or any at risk joint identified during the study period (refer to [Section 7.3.10](#)), local radiology reports should be obtained.
- Subjects meeting criteria (subjects who had Kellgren-Lawrence Grade 3 or 4 osteoarthritis of any knee or hip at Screening/Baseline, refer to [Section 7.3.11](#)) should be scheduled for magnetic resonance imaging of each hip and knee.

##### **6.4.1.1. Early Termination Follow-up Visit 1 (8 weeks after last dose of SC investigational product treatment)**

- Adverse events review.
- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.
- WPAI:OA.
- EQ-5D-5L.
- TSQM (v.II).
- mPRTI.
- Lower Extremity Activity Scale (LEAS).
- Survey of Autonomic Symptoms (SAS).
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- ECG (12-lead).
- Body weight.
- General physical examination.
- Musculoskeletal physical examination.

- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required).
- Review/update of concomitant medication.
- Assess compliance with weekly IRT entries (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Monitor for violations of concomitant NSAID use.
- Review weekly joint pain scores.
- Rescue medication (acetaminophen / paracetamol) compliance review/dispense.
- Serum pregnancy test for females of childbearing potential.
- Serum and plasma retention samples.
- Blood sample for anti-tanezumab antibody assessment (refer to [Section 7.3.14](#)).
- Blood samples for PK and PD (NGF) analyses (refer to [Section 7.5](#)).
- For subjects that performed activity level monitoring via accelerometry, blood and urine samples for biomarkers (fasting if possible, urine sample should be from 2<sup>nd</sup> void of the day or after; refer to [Section 7.6](#)).
- Reminder to females of child-bearing potential to continue with contraceptive requirements.
- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect a synovial fluid sample (refer to [Section 7.5.3](#)).

**6.4.1.2. Early Termination Follow-up Phone Contact (12 weeks after last dose of SC investigational product)**

- Adverse events review.
- Review/update of concomitant medication.
- Review subject compliance with weekly IRT entries (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Rescue medication (acetaminophen / paracetamol) compliance review.

- Reminder to females of child-bearing potential to continue with contraceptive requirements.

#### **6.4.1.3. Early Termination Follow-up Visit 2 (16 weeks after last dose of SC investigational product)**

- Adverse events review.
- WOMAC (all subscales).
- Patient's Global Assessment of Osteoarthritis.
- WPAI:OA.
- EQ-5D-5L.
- Lower Extremity Activity Scale (LEAS).
- Health Care Resource Utilization.
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Musculoskeletal physical examination.
- Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required).
- Clinical laboratory tests (blood chemistry, hematology, serum 25-hydroxy vitamin D and parathyroid hormone).
- Blood sample for anti-tanezumab antibody assessment.
- Blood samples for PK and PD (NGF) analyses.
- For subjects that performed activity level monitoring via accelerometry, blood and urine samples for biomarkers (fasting if possible, urine sample should be from 2<sup>nd</sup> void of the day or after; refer to [Section 7.6](#)).
- Serum and plasma retention samples.
- Serum pregnancy test for females of childbearing potential.
- Review/Update of concomitant medication.

- Assessment of compliance with weekly IRT entries (weekly index joint pain score, weekly non-index joint pain assessment and as applicable, weekly rescue medication and weekly NSAID use entries).
- Monitor for violations of concomitant NSAID use.
- Review weekly joint pain scores.
- Rescue medication (acetaminophen / paracetamol) compliance review/dispense.
- Initiate of standard of care treatment for osteoarthritis pain at the discretion of the investigator.
- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect a synovial fluid sample (refer to [Section 7.5.3](#)).

#### **6.4.1.4. Early Termination Follow-up Phone Contact (20 Weeks after last dose of SC investigational product)**

- Adverse events review.
- Review/update of concomitant medication.
- Review subject compliance with weekly IRT entries (weekly index joint pain score, weekly non-index joint pain assessment as applicable, weekly rescue medication and weekly NSAID use entries).
- Schedule subject for follow-up radiographic assessments (X-rays) of each shoulder, hip and knee and any other major joint for which a radiograph was obtained at the Screening visit or any at risk joint identified during the study period (refer to [Section 7.3.10](#)), local radiology reports should be obtained.
- Subjects meeting criteria (subjects who had Kellgren-Lawrence Grade 3 or 4 osteoarthritis of any knee or hip at Screening/Baseline, refer to [Section 7.3.11](#)) should be scheduled for magnetic resonance imaging of each hip and knee.

**NOTE:** Follow-up radiographs and MRIs should be completed up to 30 days before and preferably, no more than 14 days after the Early Termination Follow-up Visit 3 (24 weeks after last dose of SC investigational product).

#### **6.4.1.5. Early Termination Follow-up Visit 3 (24 weeks after last dose of SC investigational product)**

- Adverse events review.
- Lower Extremity Activity Scale (LEAS).

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- Survey of Autonomic Symptoms (SAS).
  - Health Care Resource Utilization.
  - Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
  - Orthostatic blood pressure (supine/standing) measurement.
  - ECG (12-lead).
  - Musculoskeletal physical examination.
  - Neurologic exam/Neuropathy Impairment Score (referral for neurological consult if required).
  - Review/update of concomitant medication.
  - Review weekly index joint pain scores and weekly non-index joint pain assessment as applicable, weekly rescue medication and weekly NSAID use entries.
  - Blood sample for anti-tanezumab antibody assessment (refer to [Section 7.3.14](#)).
  - For subjects that performed activity level monitoring via accelerometry, blood and urine samples for biomarkers (fasting if possible, urine sample should be from 2<sup>nd</sup> void of the day or after; refer to [Section 7.6](#)).
  - If not already completed, schedule subject for follow-up radiographic assessments (X-rays) of each shoulder, hip and knee and any other major joint for which a radiograph was obtained at the Screening visit or any at risk joint identified during the study period (refer to [Section 7.3.10](#)).
  - If not already completed, subjects meeting criteria (subjects who had Kellgren-Lawrence Grade 3 or 4 osteoarthritis of any knee or hip at Screening/Baseline, refer to [Section 7.3.11](#)) should be scheduled for magnetic resonance imaging of each hip and knee.
- NOTE:** Follow-up radiographs and MRIs should be completed up to 30 days before and preferably, no more than 14 days after the Early Termination Follow-up Visit 3 (24 weeks after last dose of SC investigational product) and local radiology reports should be obtained.
- If arthrocentesis will be performed for a subject (refer to [Section 7.4.7](#)) and the subject has provided the applicable informed consent, collect synovial fluid, plasma and serum samples (refer to [Sections 7.5.1](#), [7.5.2](#) and [7.5.3](#)).

#### **6.4.2. Procedures for Subjects Undergoing Joint Replacement**

Subjects who have undergone or plan to undergo total joint replacement or other arthroplasty procedure during the study will be discontinued from investigational product.

Subjects who undergo total knee, hip or shoulder joint replacement surgery during the study (Double-blind Treatment Period or Follow-up Period) will be followed for 24 weeks after the procedure as part of a separate protocol (Study A4091064), provided the subject consents.

Transition procedures into Study A4091064 are determined by the timing of total joint replacement surgery:

- Subjects who have undergone or plan an immediate total knee, hip or shoulder joint replacement will be discontinued from the Double-Blind Treatment period and enter into the total joint replacement follow-up protocol (Study A4091064). At the discontinuation visit, all procedures scheduled for the Week 56 and Week 64 visits should be completed unless the Subject has already completed the Week 56 and Week 64 visits, in which case only Week 80 procedures will be required. In addition, if the Week 56 visit was not completed prior to termination, a general physical examination, body weight, WPAI:OA, EQ-5D-5L, TSQM v.II and mPRTI will also be obtained. Applicable Study A4091064 Baseline Visit activities should be completed on the same day as the Study A4091058 End of Treatment Visit.
- Subjects who plan to undergo total knee, hip or shoulder joint replacement during the study will be discontinued from the Double-blind Treatment Period and entered into Early Termination Follow-up (See [Section 6.4](#)) until their joint replacement procedure. For these subjects, a complete early termination visit should be conducted prior to the total joint replacement (See [Section 6.4](#)) and entrance into Study A4091064. Study A4091064 Baseline Visit activities should be completed on the same day as the Study A4091058 early termination visit. Subjects who have not undergone or scheduled total joint replacement surgery within the investigational product or safety follow-up period of this study will not be eligible for Study A4091064.

Subjects who undergo other types of joint replacement surgery or arthroplasty during the study should be discontinued from investigational product and complete the protocol specified Safety Follow-up Period, but not be entered into Study A4091064 for follow-up.

##### **6.4.2.1. Total Joint Replacement Follow-up Protocol**

As part of the total joint replacement follow-up protocol, all source documents from the surgical procedure (including any prior orthopedic consultations and pre-operative assessments), immediate post-operative recovery, and follow-up therapy will be collected. In addition, the surgeon will be asked to complete an assessment of procedural difficulty. Imaging studies of the affected joint (such as X-rays and MRI scans) will be collected. Instructions regarding pathology specimens will be provided.

## 7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

### 7.1. Subject Diary Assessments

#### 7.1.1. Daily/Weekly Pain Assessments

If possible diary assessments of pain in the index joint and assessment of the major non-index joints will be completed by the subject at approximately the same time each day (or each week). Average pain will be assessed with an 11-point Numeric Rating Scale (NRS) ranging from zero (no pain) to 10 (worst possible pain) captured through IRT. The subjects should describe their pain in the index joint (and non-index joint when applicable) during the past 24 hours by choosing the appropriate number from 0 to 10. If possible, subjects should conduct the self-assessment in the evening prior to midnight.

#### Index Joint Pain Assessment

Average pain in the index joint will be assessed by the subject daily from the beginning of the IPAP to the Week 16 Visit, followed by weekly beginning after the Week 16 visit through Week 80 (and weekly during the Early Termination Follow-Up Period).

- Example question when the identified index joint is the right knee:

Select the number that best describes your average pain in your index joint, the right knee in the past 24 hours:

0      1      2      3      4      5      6      7      8      9      10

No  
Pain

Worst Possible  
Pain

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- Example question when the index joint is the right hip:

Select the number that best describes your average pain in your index joint, the right hip in the past 24 hours:

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

#### Non-index Joint Pain Assessment

On a weekly basis beginning at the Initial Pain Assessment Period and through Week 80 of the study (and weekly during the Early Termination Follow-Up Period), subjects will also be asked if he/she experienced new onset or increased pain in any major non-index joint. A major joint is defined as a mobile synovial joint in the limbs such as shoulders, elbows, wrists, hips, knees, ankles and excluding the joints of the toes and hands. If a subject responds that he/she has experienced new onset or increased pain in a non-index joint or other major joint (post-baseline), the subject will be asked to rate his/her pain in that joint on the same 11-point numeric rating scale shown above and will be asked to rate his/her pain in that joint for the remainder of the study.

#### **7.1.2. Rescue Medication and Amount**

Rescue medication use will be collected daily via IRT from the beginning of the IPAP to the Week 16 Visit. The dosage strength of the acetaminophen tablets/caplets/capsules will be captured. The subject should note the number of tablets/caplets/capsules of rescue medication taken during the last 24 hours.

Following the Week 16 visit up to the Week 80 visit and during the Early Termination Follow-Up Period for subjects who enter this phase of the study, the use of acetaminophen / paracetamol as rescue medication will be collected once weekly using IRT. The subject will record the number of days rescue medication was used and maximum number of tablets, capsules or caplets of rescue medication taken on any day in the past week.

#### **7.1.3. Concomitant NSAID Use**

Use of over-the-counter or prescription NSAID use will be collected weekly via IRT from the Baseline (Day 1) visit until the Week 80 visit. During the Early Termination Follow-Up Period for subjects who enter this phase of the study, the use of over-the-counter or prescription NSAID will be collected once weekly using IRT. Subjects will record the number of days of NSAID use in the past week using IRT. At telephone or clinic visits, sites will interview the subject regarding their NSAID use and record additional information, such as the medication name, dosage and reason for use on a CRF. The investigator or designee should closely monitor for concomitant NSAID use. Subjects reporting concomitant NSAID use will be managed per guidance provided in [Section 5.8.1](#).

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## 7.2. Study Visit Efficacy Assessments

### 7.2.1. Western Ontario and McMaster Universities Osteoarthritis Index

A copy of the WOMAC<sup>44</sup> Osteoarthritis NRS Index is provided in [Appendix 4](#). The WOMAC subscales will be recorded via IRT at relevant study visits.

#### 7.2.1.1. WOMAC Pain Subscale

The WOMAC Pain subscale questionnaire is to be completed by subjects at Screening, Baseline (Day 1), prior to SC dosing and Weeks 2, 4, prior to SC dosing on Weeks 8, 16 (Primary Efficacy Endpoint), 24, 32, 40 and 48 and on Weeks 56 and 64 or at Early Termination (as described in [Section 6.4](#)).

At Screening and for the remainder of a subject's participation in the study, a WOMAC pain subscale questionnaire will only be completed for the index knee or hip.

The WOMAC Pain subscale is comprised of 5 questions regarding the amount of pain experienced due to osteoarthritis in the index joint (selected study knee or hip) in the past 48 hours. The WOMAC Pain subscale is calculated as the mean of the scores from the five individual questions, which may not be a whole (integer) number. The WOMAC Pain subscale NRS scores for each question, and the WOMAC Pain subscale score, range from 0 to 10, with higher scores indicating higher pain.

#### 7.2.1.2. WOMAC Physical Function Subscale

Subjects will complete the WOMAC Physical Function subscale questionnaire at Screening, Baseline (Day 1) prior to SC dosing and Weeks 2, 4, prior to SC dosing on Weeks 8, 16 (Primary Efficacy Endpoint), 24, 32, 40 and 48 and on Weeks 56 and 64 or at Early Termination (as described in [Section 6.4](#)).

At Screening and for the remainder of a subject's participation in the study, a WOMAC Physical Function subscale questionnaire will only be completed for the index knee or hip.

The WOMAC Physical Function subscale is comprised of 17 questions regarding the degree of difficulty experienced due to arthritis in the index joint (selected knee or hip) in the past 48 hours. The WOMAC Physical Function subscale is calculated as the mean of the scores from the seventeen individual questions, which may not be a whole (integer) number. The WOMAC Physical Function subscale NRS scores for each question, and the WOMAC Physical Function subscale score, range from 0 to 10 with higher scores indicating worse function. This refers to the subject's ability to move around and perform usual activities of daily living.

#### 7.2.1.3. WOMAC Stiffness Subscale

Subjects will complete the WOMAC Stiffness subscale questionnaire at Screening, Baseline (Day 1) prior to SC dosing and Weeks 2, 4, prior to SC dosing on Weeks 8, 16 (Primary Efficacy Endpoint), 24, 32, 40 and 48 and on Weeks 56 and 64 or at Early Termination (as described in [Section 6.4](#)).



indicate greater impairment and less productivity. The WPAI-OA is self-administered by the subject and takes less than 5 minutes to complete ([Appendix 6](#)).

#### **7.2.4. EuroQol 5 Dimension (EQ-5D-5L)**

The EQ-5D-5L™ will be completed prior to SC dosing at Baseline (Day 1) and prior to SC dosing at Weeks 8, 16, 24, 40, 56 and 64 (or at Early Termination as described in [Section 6.4](#)). Subjects will record their responses using IRT.

The EQ-5D-5L™ is a subject completed questionnaire designed to assess the subject's current health and translate that score into an index value or utility score. Health status is described in terms of 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. There are two components to the EQ-5D-5L™: a Health State Profile and a visual analog scale (VAS) item. The 5 item health state profile will be assessed to calculate a single index value (see [Appendix 7](#)). This instrument provides a mechanism for conducting cost-effectiveness and cost-utility analyses.<sup>46</sup>

#### **7.2.5. Treatment Satisfaction Questionnaire for Medication v.II (TSQM)**

Subjects will complete the Treatment Satisfaction Questionnaire for Medication v.II ([Appendix 13](#)) at Weeks 16 and 56 (or at early termination, as described in [Section 6.4](#)). Subjects will record their responses using IRT.

The Treatment Satisfaction Questionnaire for Medication (TSQM v.II) is an 11-item validated scale that quantifies the subject's level of satisfaction with study medication, effectiveness and side effects/tolerability. Most items are scored on a 7-point Likert scale ranging from 'Extremely Satisfied' to 'Extremely Dissatisfied'. The domains of Effectiveness, Side Effects, Convenience and Global Satisfaction are scored from 0-100 with a higher score indicating greater satisfaction. The TSQM v.II is self-administered by the subject and takes less than 5 minutes to complete.<sup>47</sup>

#### **7.2.6. Patient Reported Treatment Impact Assessment-modified (mPRTI)**

The mPRTI is a self-administered questionnaire containing three items to assess patient satisfaction, previous treatment, preference and willingness to continue using the study medication. Higher scores indicate greater satisfaction, preference or willingness to use the study medication; see [Appendix 16](#). Subjects will record their responses using IRT.

The questionnaire will be completed by the subject at Weeks 16 and 56 and at Early Termination (refer to [Section 6.4](#)).

#### **7.2.7. Assessment of Health Care Resource Utilization**

The utilization of health care resources (eg, doctor office visits, hospitalizations, surgeries or procedures, etc.) during the 3 months prior to Baseline will be assessed by questionnaire at Baseline (Day 1). In addition, Health Care Resource Utilization will be collected at study visits at Weeks 64 and 80 (or at early termination, as described in [Section 6.4](#)). Subjects will record their responses using IRT.

### 7.3. Safety Assessments

Each subject will provide a general medical history as well as a detailed musculoskeletal/joint specific medical history. The information will be recorded on the appropriate CRF(s) at Screening. Information on prior medications (within 30 days of the Screening Visit for non-analgesic medications, 12 months for pain and other medications for the treatment and relief of symptoms of osteoarthritis), non-pharmacologic therapies, supplements and concomitant medication use will be collected at Screening and concomitant medication at each scheduled study visit. Information regarding tobacco and alcohol use and dependency will also be collected at Screening.

#### 7.3.1. General Physical Examination

Each subject will undergo a general physical examination at Screening and Week 56, or at Early Termination (as described in [Section 6.4](#)).

#### 7.3.2. Musculoskeletal History and Physical Examination

Each subject will also undergo a musculoskeletal physical examination at Screening, Baseline (Day 1), and at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64 and 80 (or at Early Termination, as described in [Section 6.4](#)).

At Screening, the investigator should collect a thorough musculoskeletal history. The investigator should inquire about current and past history of osteoarthritis, ligament tear or rupture, joint surgeries (including arthroscopic procedures), fractures, gout, osteoporosis, osteopenia, joint injuries or other conditions.

At each visit, the investigator will conduct a thorough musculoskeletal physical examination of all major joints. The musculoskeletal physical examination should evaluate the joints for swelling, redness, tenderness, deformity, osteophytes or nodes, crepitus and pain on motion and will be documented on the CRF. The investigator should also collect subject-reported information on any current joint symptoms including pain, stiffness, and swelling. Any clinically significant change in symptoms or the examination should be reported as an adverse event.

#### 7.3.3. Laboratory Safety Assessments

Blood and urine tests for safety assessments and/or determination of eligibility will be performed as indicated in this table and described in the subsections below:

Chemistry	Hematology	Other	Urinalysis
<u>Screening, Baseline (Day 1), Weeks 16 and 64 (or Early Termination Visit 2):</u> Sodium, potassium, chloride, bicarbonate, glucose (non fasting), Blood Urea Nitrogen (BUN), creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, cholesterol, triglycerides, gamma glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LDH), alkaline phosphatase, creatinine phosphokinase (CPK), and uric acid	<u>Screening, Baseline (Day 1), Weeks 16 and 64 (or Early Termination Visit 2):</u> Complete blood count with differential	<u>Screening only:</u> HbA1c Hepatitis screen (eg, HBsAg, Anti-HCV), HIV test (HIV Ab screen)  Urine toxicology screen (eg, for opiates, barbiturates, amphetamines, cocaine, propoxyphene, methadone, phencyclidine, and methaqualone).  Serum FSH if applicable  <u>Screening, Weeks 56 and 64 (or Early Termination Visits 1 and 2):</u> Serum Pregnancy Test  <u>Baseline, Weeks 8, 16, 24, 32, 40 and 48 (Prior to dosing at Dosing Visits):</u> Urine Pregnancy Test  <u>Baseline, Weeks 16, 56 and 64 (or Early Termination Visits 1 and 2):</u> Serum and plasma retention samples  <u>Baseline, Week 64 (or Early Termination Visit 2)</u> Serum 25-OH Vit D, serum parathyroid hormone (PTH)	<u>Screening only:</u>  pH, protein, glucose, ketones, blood, bilirubin, nitrite, specific gravity and leukocytes.  Microscopic analysis performed if abnormalities are present on the above components.
Does not include PK, PD (NGF), Anti-tanezumab Antibodies, biomarker or synovial fluid (refer to sections below for collection details)			

### 7.3.3.1. Blood Tests

Blood tests for clinical laboratory testing (chemistry, hematology) will be performed at Screening, Baseline (Day 1) and Weeks 16 and 64 (or at Early Termination, as described in [Section 6.4](#)). An unscheduled visit(s) may be necessary for follow-up of abnormal test results.

Serum and plasma retention samples will be collected at Baseline (Day 1), Weeks 16, 56 and 64 or at Early Termination (as described in [Section 6.4](#)).

See [Section 7.3.3.3](#) for sample collected for serum pregnancy test and [Section 7.3.3.4](#) for sample collected for FSH testing.

Blood samples collected for PK, PD (NGF), biomarkers and anti-tanezumab antibody measurements are described in [Sections 7.5.1, 7.5.2, 7.6 and 7.3.14](#).

Synovial fluid samples collected for PK, PD (NGF) are described in [Section 7.5.3](#).

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### 7.3.3.2. Urinalysis and Urine Toxicology Screen

Urinalysis and urine toxicology screen will be performed at Screening only.

Urine samples collected for biomarker analyses are described in [Section 7.6.2](#).

### 7.3.3.3. Pregnancy Tests

For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed during the Screening period, reviewed and confirmed as negative. A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the double-blind treatment period (or when potential pregnancy is otherwise suspected), and repeated at Visits at Weeks 56 and 64 or at Early Termination as described in [Section 6.4](#) to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Qualitative urine pregnancy tests must be sensitive to at least 25 mIU/mL. These tests will be performed prior to dosing with SC investigational product at Baseline (Day 1), and Weeks 8, 16, 24, 32, 40 and 48. Qualitative point-of-service urine pregnancy tests will be conducted with the test kit approved by the sponsor in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the qualitative point-of-service urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

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Refer to [Sections 8.10](#) and [8.10.1](#) for guidance pertaining to exposure during pregnancy and post-natal follow-up.

### 7.3.3.4. Serum FSH Testing

Female subjects of non-childbearing potential who have not had a hysterectomy or bilateral oophorectomy and who have been amenorrheic for at least 1 year with no alternative pathological or physiological cause must undergo serum FSH testing to determine post-menopausal status. A serum FSH level within the laboratory's reference range for post-menopausal females is required. Female subjects who have been amenorrheic less than 1 year will be considered of child-bearing potential. Female subjects of childbearing potential do not require serum FSH testing.

### **7.3.4. Assessment of Pain in Major Joints at Screening with Numeric Pain Scale Rating (NRS)**

Average pain in the major joints (bilateral shoulders, hips and knees) or any other painful, major joint that will be imaged at Screening, will be assessed by the subject at the Screening Visit with an 11-point Numeric Rating Scale (NRS) ranging from zero (no pain) to 10 (worst possible pain) and captured using IRT.

### **7.3.5. Vital Signs**

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate) will be collected and recorded throughout the study at Screening, prior to SC dosing at Baseline (Day 1) and on Weeks 2, 4, 8, 16, 24, 32, 40 and 48, and at Weeks 56, 64 and 80 (or at Early Termination, as described in [Section 6.4](#)). Vital signs will be collected after the subject has been in a sitting position for at least five minutes at each noted visit.

#### **7.3.5.1. Orthostatic Blood Pressure Measurement**

In addition to sitting vital sign measurements, orthostatic blood pressure measurements will be obtained using a standard manual sphygmomanometer at Screening, Baseline/Day 1 and at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64 and 80 (or at Early Termination, as described in [Section 6.4](#)). At each of these clinic visits, blood pressure will be assessed in supine and standing positions. Orthostatic blood pressure measurements will be obtained after collection of the sitting vital signs and before any required phlebotomy (and prior to dosing at dosing visits). To minimize chances of orthostatic hypotension related to volume depletion, subjects should be reminded to report for clinic visits well hydrated. In this regard, investigators could consider recommending to subjects that they consume 8-16 ounces (240-480 mL) of water prior to reporting to the clinic for study visits. All orthostatic blood pressure measurements will be recorded in the IRT system.

Supine blood pressure measurement will be obtained after subjects have been in the supine position for a minimum of 10 minutes. To ensure that a stable supine blood pressure measurement is obtained, at least two systolic and diastolic measurements will be performed. If the replicate systolic and diastolic measurements differ by no more than 10 mmHg and 5 mmHg, respectively, the supine blood pressure will be considered to be stable. The mean of the two stable replicate measures will be considered to represent the baseline supine blood pressure (mean systolic and mean diastolic blood pressure) for that visit. Once the supine blood pressure is considered to be stable, subjects will be asked to assume the standing position. After subjects have been in the standing position for 1 minute and 3 minutes, systolic and diastolic blood pressure will be measured and recorded for both time points. If the measurements do not meet the criteria for orthostatic (postural) hypotension, no further measurements are needed. If either the 1 minute or 3 minute standing BP measurements show decreases meeting the criteria shown in [Table 9](#), the sequence of supine and standing measurements should be repeated up to 2 more times. Refer to [Table 9](#) for the criteria defining orthostatic hypotension and actions that should be taken when orthostatic hypotension criteria are met.

**Table 9. Orthostatic Blood Pressure Changes and Subject Management**

Mean Supine Systolic Blood Pressure	Decrease in Blood Pressure Defining Orthostatic (postural) Hypotension	Actions (for both criteria)
≤150 mmHg  OR >150 mmHg	≥20 mmHg systolic or ≥10 mmHg diastolic  ≥30 mmHg systolic or ≥15 mmHg diastolic	- Repeat the sequence of measurements (supine and standing) up to 2 times. If either the 1 minute or 3 minute standing BP meets the orthostatic (postural) hypotension criteria, then that sequence is considered positive. If 2 of 2 or 2 of 3 sequences are positive, then orthostatic hypotension is considered confirmed and an adverse event of orthostatic hypotension will be reported.  - Refer to <a href="#">Section 7.4.3</a> for subject management and dosing guidance.

Refer to [Section 7.4.3](#) for guidance on determining which subjects with confirmed orthostatic hypotension will require consultation with a neurologist or cardiologist.

### 7.3.6. 12-Lead Electrocardiogram

A 12-lead ECG will be performed at Screening for determination of ECG-related eligibility. Additional 12-Lead ECGs will be performed at Weeks 56 and 80 (or at Early Termination, as described in [Section 6.4](#)). Post-Screening ECGs may be collected if needed (for cause), at the discretion of the investigator.

A 12-lead ECG should be recorded after subjects have been resting at least 5 minutes in the supine position in a quiet environment. Digital ECG tracings will be performed using equipment from and analyzed by a central ECG laboratory. All standard intervals (PR, QRS, QT, QTcF, QTcB, RR intervals and HR) will be collected. The QTc interval reading produced by machine will be listed in the data listings. The QT interval will be manually measured by the central laboratory. The cardiologist at the central ECG laboratory reading the ECGs will be blinded regarding investigational product assignment. In the event a clinically significant ECG abnormality is seen at a visit on an ECG obtained for cause (post-treatment), the investigator should consider evaluation of the subject by a cardiologist.

Investigators will also be alerted of subjects with evidence of the following as a potential indicator of sympathetic nervous system dysfunction:

- Significant bradycardia (heart rate of ≤45 beats per minute (BPM) on an ECG, exclusionary at Screening).
- Heart rate decrease from Screening of ≥25% with resulting heart rate <60 BPM.

Investigators should report adverse events of bradycardia for subjects who meet the ECG criteria listed above. Refer to [Section 7.4.3](#) for additional details pertaining to subject

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evaluation and further dosing with investigational product in subjects with sympathetic function adverse events.

### **7.3.7. Survey of Autonomic Symptoms (SAS)**

The Survey of Autonomic Symptoms (SAS) is a validated, easily administered instrument to measure autonomic symptoms that has been proposed to be valuable in assessing neuropathic autonomic symptoms in clinical trials (refer to [Appendix 15](#)).

Subjects will complete the SAS at Screening, prior to SC dosing at Week 24, and at Weeks 56 and 80 (or at Early Termination, as described in [Section 6.4](#)). Subjects will enter responses in IRT.

### **7.3.8. Lower Extremity Activity Scale (LEAS)**

Subjective assessments of subject activity will be assessed in all subjects participating in the study using the Lower Extremity Activity Scale (LEAS).<sup>48</sup> The LEAS is a single item, self administered scale that was developed and validated to assess actual activity level in subjects having total knee arthroplasty (refer to [Appendix 12](#)).

The LEAS scale was designed to reflect four major levels of lower-extremity activity (1) housebound (essentially unable to walk or a minimal ability to walk), (2) more ordinary walking about the house, (3) walking about the community, and (4) walking about the community as well as substantial work or exercise. The instrument relies upon 12 questions with three of these questions having three levels of response that permit finer gradation at the high end of physical activity. The resulting, 18-level scale allows subjects to select a single description that most represents his or her self-perceived activity level. The final score is simply the number of the descriptor selected by the subject as being most representative of his or her activity level. The minimum possible score is 1 (entirely bedbound) and the maximum possible score is 18 (currently competitive athlete).

Subjects will complete the LEAS prior to SC dosing at Baseline (Day 1) and on Weeks 8, 16 and 24, and at Weeks 4, 56 and 80 (or at Early Termination, as described in [Section 6.4](#)). Subjects will enter responses in IRT or a subject worksheet.

### **7.3.9. Activity Level Monitoring (Actigraphy)**

Subject activity level will be assessed using actigraphy in subjects at selected sites (to recruit a maximum of 360 subjects) in three separate monitoring periods. The monitoring periods will occur during the Screening period (Stage 2) and at approximately Weeks 16 and 56. During the Screening period, actigraphy over 7 consecutive days may take place anytime during the 2-week, pre-randomization NSAID regimen stabilization and prohibited drug washout periods and in parallel with the IPAP. Accelerometry to be completed prior to the Week 16 and Week 56 visits will take place over two separate, 14 consecutive day monitoring periods between Week 14 and the Week 16 visit and between Week 54 and the Week 56 visit, respectively.

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Prior to each monitoring period, subjects will be instructed how to wear the accelerometer and to put the accelerometer on upon arising in the morning, and to wear the accelerometer continuously (except for water activities) until going to bed at night for 7 or 14 consecutive days (depending on the monitoring period) while going about their usual daily activities. Subjects will also be encouraged to maintain a log (electronic or written) to record when the accelerometer was put on in the morning and removed at night (or if removed for any other purpose).

### 7.3.10. Radiographic Assessments

Scheduled radiographics of each shoulder, hip and knee will be obtained at Screening and at the Week 24, 56 and 80 (or at Early Termination, as described in [Section 6.4](#)) visits. Radiographic assessments of other major joints exhibiting signs or symptoms suggestive of osteoarthritis should also be imaged. A major joint is defined as a mobile synovial joint in the limbs such as shoulders, elbows, wrists, hips, knees, ankles and excluding the joints of the toes and hands. Any joint imaged at Screening or other at-risk joints identified during the study period should also be imaged at Week 24, 56 and 80 (or at Early Termination, as described in [Section 6.4](#)) visits.

**NOTE:** It is recommended that the radiographs required at Screening be obtained as soon as possible after the Screening visit (Stage 1) to permit central radiology review of the images for determination of subject radiographic eligibility to proceed to Screening Stage 2 procedures and for initial dosing in the study. Subjects will not be permitted to start dosing in the study until the Screening radiographs are reviewed by the Central Reader and eligibility is established. Radiographs required for the Week 24 visit may be conducted up to 30 days before the visit, but it is recommended that the Week 24 radiographs be obtained at least two weeks prior to the Week 24 visit to permit Central Reader review of the images and to establish eligibility for continuation in the study. Radiographs required for the Week 56 visit may be conducted within 30 days of the visit (ie, before or after the visit). Radiographs for the Week 80 visit may be conducted up to 30 days before and preferably, no more than 14 days after the visit.

For subjects who are discontinued prior to the Week 56 visit, follow-up radiographs of each shoulder, hip and knee (and any other major joint imaged at Screening or other at risk joints identified during the study period) should be performed as soon as possible (refer to [Section 6.4](#)) after the decision to withdraw from the study has been made, provided at least 30 days have passed since the last set of X-rays were collected. A final set of follow-up radiographs of each knee, hip and shoulder (and any other major joint imaged at Screening or other at risk joints identified during the study period) should be obtained 24 weeks (Early Termination Visit 3, [Section 6.4.1.5](#)) after the last dose of SC investigational product was administered.

If a local radiology reading was performed for X-rays obtained in the study, the local radiology report should be obtained and provided to Pfizer or its designee (eg, the radiology Central Reader).

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The X-ray technologists, in addition to their professional training and certifications, will be trained in performing the radiographic protocols for the knees, hips, and shoulders for this study and given approval by Pfizer or its representative to perform study X-rays. To facilitate reproducibility and accuracy of joint space width measurement in the knees, a semi-automated software and positioning frame will be utilized. The Core Imaging Laboratory will be responsible for working with the sites to ensure quality, standardization and reproducibility of the radiographic images/assessments made at the Screening and follow-up time-points. Additional details regarding the required X-rays will be provided in a site imaging manual.

Central radiology readers (Central Readers) will be board certified radiologists or have the international equivalent as musculoskeletal radiologists. The Central Readers will be governed by an imaging atlas and an imaging Charter which includes a specific description of the scope of their responsibilities. Central Readers will review radiology images at Screening for assessment of eligibility (including determination of Kellgren-Lawrence Grade) and identification of exclusionary joint conditions such as rapidly progressive osteoarthritis, atrophic or hypotrophic osteoarthritis, subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis and pathological fractures. After randomization, Central Readers will review radiology images for diagnosis of joint conditions that would warrant further evaluation by the Adjudication Committee such as possible or probable rapidly progressive osteoarthritis, subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis or pathological fracture and for subjects undergoing total joint replacement for any reason, all images and other source documentation will be provided to the blinded tanezumab Adjudication Committee for review and adjudication of the event. The Adjudication Committee's assessment of the event will represent the final classification of the event.

### 7.3.10.1. Radiation Exposure

The International Commission on Radiation Protection (ICRP) has developed and applied the ALARA principle in developing guidelines that balance the benefits of radiation exposures against possible risks. This principle states that human exposures to radiation should be "As Low As Reasonably Achievable, with economic and social considerations taken into account."

Within the context of medical and research exposures, this is usually taken to mean that each individual should receive no more radiation than is necessary to obtain reliable information and that no more research participants should be irradiated than is necessary to answer a particular scientific question.

Radiograph	Annual Effective dose (mSv)
Knee <sup>31</sup>	0.024 mSv
Hip <sup>49,50</sup>	1.9 mSv
Shoulder <sup>49</sup>	0.04 mSv
TOTAL	1.964 mSv

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Subject annual exposure per body part imaged is shown in the table above. The annual total effective dose per subject in this study is expected to be approximately 2.0 mSv. This can be compared to the annual effective dose from natural background radiation of approximately 3.0 mSv.<sup>52</sup> In some cases, it is expected that a repeat image of a joint may be necessary due to the quality of the X-ray images. Subjects requiring a DXA scan will receive an additional radiation dose of approximately 0.025 mSv.<sup>52</sup>

### 7.3.11. Magnetic Resonance Imaging (MRI)

All subjects who advance to the Stage 2 Screening visit (refer to [Section 6.1.2](#)) will have MRI of each hip and knee. For subjects who are determined by the Central Reader to have Kellgren-Lawrence Grade 3 or 4 osteoarthritis in any knee or hip in the Screening radiographs, follow-up MRIs of each hip and knee will be performed at Weeks 24, 56 and 80 (or at early Termination, as described in [Section 6.4](#)).

In addition to obtaining MRIs at scheduled time points specified above, investigators and the Central Reader may request an MRI to further evaluate subjects who present with severe and persistent joint pain or to confirm or further evaluate image findings recorded in a locally read radiology report. The Central Reader will review MRI images that were obtained to further evaluate subjects who present with severe and persistent joint pain or to confirm or further evaluate suspect image findings for diagnosis of joint conditions that would warrant further evaluation by the Adjudication Committee such as possible or probable rapidly progressive osteoarthritis, subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis or pathological fracture.

Additional details regarding the required MRIs will be provided in a site imaging manual.

### 7.3.12. Dual Energy X-ray Absorptiometry (DXA) Scan

Dual Energy X-ray Absorptiometry scans of the hip and lumbar spine, will be performed for subjects meeting National Osteoporosis Foundation recommendations for bone mineral density testing who advance to the Stage 2 Screening Visit (refer to [Section 6.1.2](#)). Typically the left hip will be scanned, in the event that the left hip cannot be scanned (eg, prosthetic hip in place) the right hip will be scanned.

National Osteoporosis Foundation recommendations for bone mineral density testing:

1. All females  $\geq 65$  yrs of age.
2. Post-menopausal females and men (50-69 yrs) with risk factors (refer to [Appendix 10](#)).
3. Men  $\geq 70$  yrs.
4. In post-menopausal women and men age 50 and older who have had an adult age fracture (major skeletal sites excluding fractures of the fingers, toes, facial bones and skull).

In addition, to the above:

1. All subjects with a medical history of osteoporosis or receiving bisphosphonates at the screening visit will be required to have DXA scans during Stage 2 of the screening process.

Additional details regarding the required DXA scans will be provided in a site imaging manual.

### 7.3.13. Neurologic Examination

Neurologic examinations will be performed by a designated physician and assessed for clinically significant changes from Baseline. The examinations will be performed at Screening, Baseline, and Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64 and 80 (or at Early Termination, as described in [Section 6.4](#)) and the Neuropathy Impairment Score (NIS) will be completed at these time points based on this neurological exam (refer to [Appendix 8](#)). Neurologic examination will assess strength of groups of muscles of the head and neck, upper limbs and lower limbs, deep tendon reflexes and sensation (tactile, vibration, joint position sense and pin prick) of index fingers and great toes in order to complete the NIS. The NIS is a standardized instrument which has been tested in both healthy subjects and patients with neuropathy and which has been used to evaluate subjects for signs of peripheral neuropathy in clinical trials.<sup>53</sup> Investigators and other designated physicians performing the neurologic evaluations are required to attend a training session for neurological exam in order to apply consistency across sites. The neurological exams must be performed in a controlled and consistent manner and by the same examiner when possible.

A neurologic evaluation should be performed by a consulting neurologist if any of the following occurs:

- If an adverse event suggestive of new or worsening peripheral neuropathy or an adverse event of abnormal peripheral sensation (eg, allodynia, burning sensation, carpal tunnel syndrome, dysesthesia, hyperesthesia, hyperpathia, hypoesthesia, neuralgia, neuritis, neuropathy peripheral, pallesthesia, paresthesia, peripheral sensory neuropathy, sciatica, sensory disturbance, sensory loss, tarsal tunnel syndrome) reported as: 1) a serious adverse event or 2) an adverse event which has resulted in the subject being withdrawn from the study, or 3) an adverse event ongoing at the end of the subject's participation in the study, or 4) an adverse event of severe intensity.
- A new or worsened clinically significant abnormality on the neurologic exam should be reported as an adverse event and may result in a neurologic evaluation/consult further to the guidance above.
- A neurological adverse event which is non-neuropathic (eg, stroke, seizure) but which the investigator considers medically important should also result in a neurological consultation.



be allowed. Subjects experiencing these types of reactions will enter the Early Termination Follow-up period (refer to [Section 6.4](#)).

Severe hypersensitivity reactions are defined as those causing anaphylaxis. Severe injection site reactions are defined as those in which ulceration or severe necrosis occurs.

### 7.4.3. Orthostatic Hypotension and Sympathetic Function Adverse Events

Blood pressure changes meeting the pre-specified criteria for orthostatic hypotension and confirmed as described in [Section 7.3.5.1](#) will be designated as confirmed orthostatic hypotension episode and should be reported as an adverse event whether or not the subject had accompanying symptoms.

Confirmed episodes of orthostatic hypotension: If a confirmed episode of orthostatic hypotension occurs (as defined in [Section 7.3.5.1](#)) it should be reported as an adverse event and the subject should be further evaluated as described below to determine if a neurology or cardiology consultation should be obtained and/or whether further treatment with investigational product should occur. [Figure 2](#) provides a flow diagram for the process described below.

1. If no apparent medical cause (eg, dehydration, illness, medications) is identified at the time the orthostatic hypotension criterion is met and the subject is symptomatic, the subject should be further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible. See “Sympathetic function adverse events” below for decisions regarding subject management and continued dosing with investigational product.
2. If an apparent medical cause is identified at the time the orthostatic hypotension criterion is met or if the subject is asymptomatic, the subject should have a repeat assessment of orthostatic hypotension performed at least 1 week later but not more than 4 weeks later. During this time the investigator should attempt to address the underlying medical cause of the orthostatic hypotension. If confirmed orthostatic hypotension (as defined in [Section 7.3.5.1](#)) is present at the follow-up visit, the subject should be further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible. See “Sympathetic function adverse events” below for decisions regarding subject management and repeat dosing.

Sympathetic function adverse events: Subjects reporting adverse events (any seriousness or severity) with preferred terms of bradycardia (see [Section 7.3.6](#) for ECG criteria for bradycardia), syncope, orthostatic hypotension (as described above and in boxes C and E of flow diagram, [Figure 2](#)), anhidrosis or hypohidrosis should be further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible.

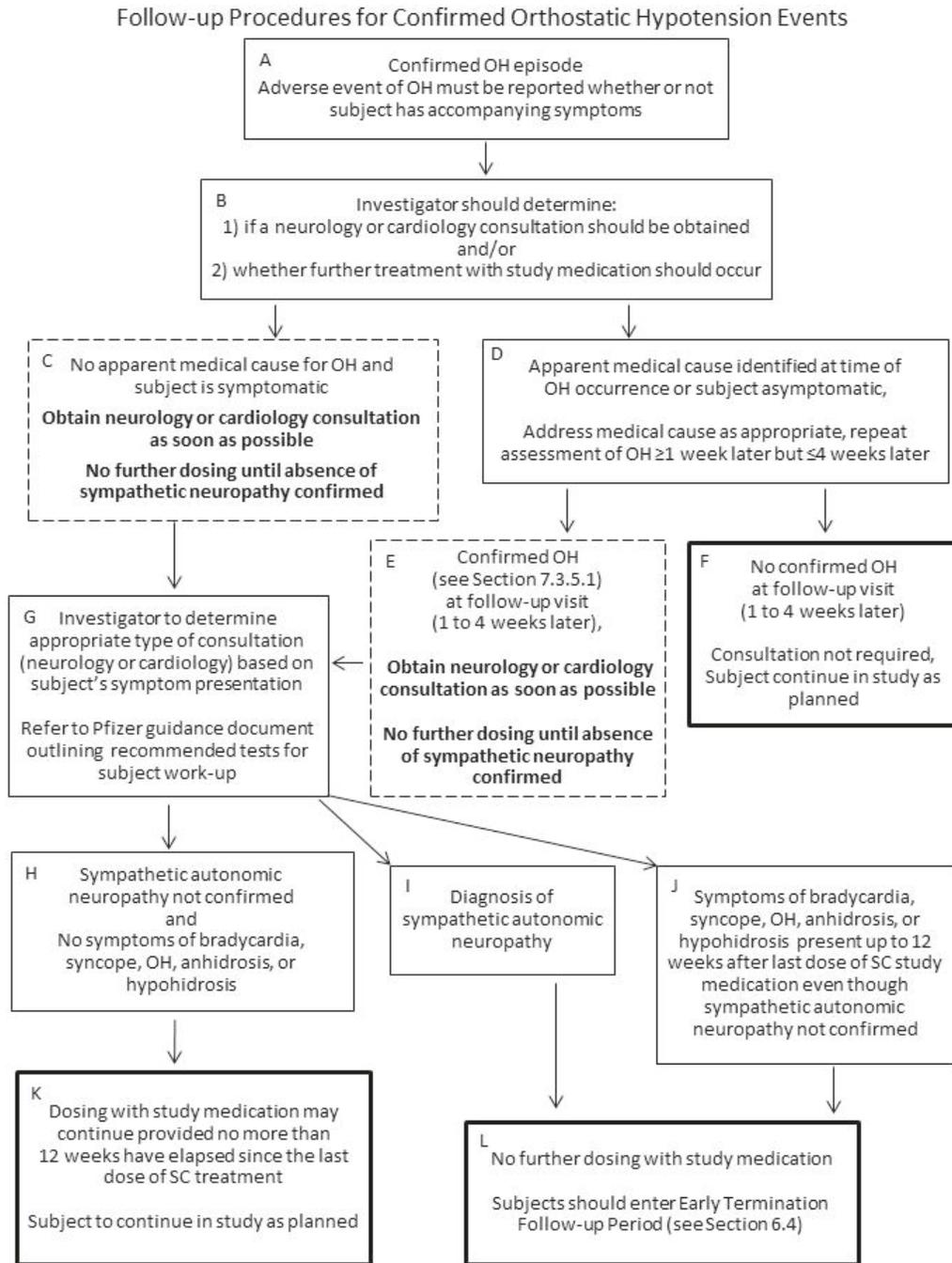
The investigator should determine the appropriate type of consultation (neurology or cardiology) depending on the subject’s symptom presentation and the investigator’s

assessment as to the specialist best able to evaluate the subject. Pfizer will provide a guidance document which outlines appropriate recommendations regarding tests to consider for subject work-up.

These subjects should not be dosed with SC investigational product until the absence of sympathetic autonomic neuropathy has been confirmed. Subjects who are not deemed to have a sympathetic autonomic neuropathy based on this evaluation can continue the study provided no more than 12 weeks have elapsed since the last dose of SC treatment (Boxes H and K of flow diagram, [Figure 2](#)). However, if the subject is still symptomatic with bradycardia, syncope, orthostatic hypotension, anhidrosis or hypohidrosis up to 12 weeks after the last dose of SC treatment, s/he should not receive additional investigational product, even if a sympathetic autonomic neuropathy has not been confirmed (Boxes J and L of flow diagram, [Figure 2](#)), and will enter the Early Termination Follow up period (refer to [Section 6.4](#)). Subjects found to have a sympathetic autonomic neuropathy (Boxes I and L of flow diagram, [Figure 2](#)) should not receive additional investigational product and will enter the Early Termination Follow up period (refer to [Section 6.4](#)).

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**Figure 2. Follow-up Procedures for Confirmed Orthostatic Hypotension Events**



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#### 7.4.4. Evaluation and Follow-up for Increased, Severe Persistent Joint Pain

Average daily pain in the index joint (hip or knee) will be assessed with an 11-point numeric rating scale (0 to 10) and collected via IRT beginning in the IPAP through Week 16 of the study followed by weekly assessments between Weeks 16 and 80. In addition, on a weekly basis beginning at the Initial Pain Assessment Period and through Week 80 of the study, the subject will also be asked if he/she experienced new onset or increased pain in a major non-index joint (refer to [Section 7.1.1](#)). If a subject responds that he/she has experienced new onset or increased pain in a non-index joint or other major joint (post-baseline), the subject will be asked to rate his/her pain in that joint on the same 11-point numeric rating scale, using a 24-hour recall (refer to [Section 7.1.1](#)) and will be asked to rate his/her pain in that joint for the remainder of the study.

Joint pain scores recorded electronically will be monitored by site staff to identify subjects who have a pattern of severe pain over several days or a rapid increase in pain. Subjects who record increased pain scores of severe intensity (eg, a score of 7-10 out of 10 on a numerical rating scale) in a knee, hip, shoulder or other major joint which is persistent for at least 2 weeks despite treatment with analgesic medication should be evaluated by the investigator to determine the source of the subject's pain and whether more comprehensive evaluation (eg, radiographic or MRI imaging, orthopedic consultation) of the subject is warranted. An earlier evaluation of the subject can be made at the discretion of the investigator.

At each study visit, systematic site review of the WOMAC Pain Scores, electronically recorded pain scores, and relevant spontaneously reported adverse events will be implemented. In addition, adverse events of joint pain, joint swelling, joint injury/accidents, fractures or worsening of osteoarthritis symptoms in index or non-index joints will be evaluated by the site personnel. An assessment of the subjects' general health and major joints for any changes in their osteoarthritis status will be carried out.

Musculoskeletal physical exam findings, review of reported musculoskeletal adverse events, and in-clinic efficacy assessments will be recorded on specific case report forms for each study visit.

Subjects meeting the criteria for increased severe or persistent pain or with other clinically significant findings based on the assessment of the Investigator are considered to have a joint(s) at risk and must have radiographs (X-rays) of the joint(s) obtained and sent to the Central Reader for assessment. MRI scans will not be required but may be obtained if warranted for diagnostic purposes. If warranted, the subject will be referred to an orthopedic surgeon for evaluation.

Radiographic (and any MRI) images collected as part of follow-up procedures for reports of increased severe or persistent pain or clinically significant findings of the investigator will be assessed by the Central Reader for possible or probable events of rapidly progressive osteoarthritis, subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture (refer to [Section 7.4.5](#) and [Section 9.5](#)).

#### **7.4.5. Central Reader and Subject-Level Stopping Criteria for Joint Safety Events**

Subjects identified through the measures described above (in [Section 7.4.4](#)) who are determined by the Central Reader to have a possible or probable joint safety event (rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture), will be withdrawn from treatment and enter the Early Termination Follow-up period (refer to [Section 6.4](#)).

The Central Reader will review the radiology images on an ongoing basis and provide assessments to the investigator and Pfizer. For subjects who are identified with a possible or probable joint safety event described above and for subjects undergoing total joint replacement for any reason, all images and other source documentation will be provided to the blinded tanezumab Adjudication Committee for review and adjudication of the event. The Adjudication Committee's assessment of the event will represent the final classification of the event (refer to [Appendix 14](#)).

Subjects with adverse event reports of rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture, will be withdrawn from treatment and enter the Early Termination Follow-up period (refer to [Section 6.4](#)).

In addition to Subject-Level Stopping Criteria for Joint Safety Events, this study will also employ Protocol-Level Stopping Criteria. Protocol-Level Stopping Criteria for Joint Safety Events are described in [Section 9.6.2](#).

#### **7.4.6. Procedures for Subjects Undergoing Joint Replacement**

Subjects who have undergone or plan to undergo total joint replacement or other arthroplasty procedure during the study will be discontinued from investigational product. Follow-up procedures for these subjects are described in [Section 6.4.2](#). In addition, subjects who undergo total knee, hip or shoulder joint replacement surgery during the study (Treatment Period or Follow-up Period) will be followed for 24 weeks after the procedure as part of a separate protocol, provided the subject consents (refer to [Section 6.4.2.1](#)).

#### **7.4.7. Procedures for Subjects Undergoing Arthrocentesis**

If an investigator determines that arthrocentesis is necessary for a subject participating in the study, investigators are requested to submit a synovial fluid sample for exploratory analysis of synovial NGF, tanezumab and potentially biomarker concentrations.

Subjects will be asked to provide informed consent for the investigator to submit and have the synovial fluid sample analyzed and to collect and analyze additional blood samples unless the arthrocentesis is performed at a visit in which PK/PD blood samples are already being obtained. These blood samples will be used for analysis of plasma tanezumab, serum NGF and potentially biomarker concentrations.

Refer to [Sections 7.5.1](#), [7.5.2](#), [7.5.3](#) and [7.6.3](#).



Instructions regarding sample collection and processing (eg, sample volumes, tube types, storage temperatures) will be provided in the laboratory manual.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

NGF samples may be used for further evaluation of the bioanalytical methods used for measuring NGF. These data will be used for internal exploratory purposes and will not be included in the clinical report.

The shipment address will be provided to the investigator site prior to initiation of the study.

### **7.5.3. Synovial Fluid for Analysis of Tanezumab and NGF**

Providing the applicable informed consent has been obtained, synovial fluid samples for the assessment of tanezumab and NGF (See [Sections 7.5.1, 7.5.2](#)) assessments may be collected whenever an investigator performs arthrocentesis for a subject. As arthrocentesis will be performed at the discretion of the investigator, it is not a scheduled or required protocol procedure and may occur at a scheduled or unscheduled visit.

The total volume of synovial fluid that was collected as part of the procedure will be processed to accommodate the analysis of tanezumab, NGF and potentially biomarkers (refer to [Section 7.6.3](#)).

Instructions regarding sample collection and processing (eg, sample volumes, tube types, storage temperatures) will be provided in the laboratory manual.

Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

Tanezumab and NGF samples may be used for further evaluation of the bioanalytical method. This could include measurement of endogenous proteins that can bind to NGF. These data will be used for internal exploratory purposes and will not be included in the clinical report.

The shipment address will be provided to the investigator site prior to initiation of the study.

## **7.6. Biomarkers**

### **7.6.1. Serum Biomarkers**

Blood samples for the assessment of biomarkers that can be modulated by osteoarthritis will be collected at Baseline (Day 1; pre-dose), Week 8 (pre-dose), and Week 16 (pre-dose) for all subjects.

For subjects that will have activity level monitoring via accelerometry (N ~360), additional biomarker samples will be collected at Week 32 (pre-dose), Week 48 (pre-dose), and at Weeks 56, 64, 80 (or at Early Termination, as described in [Section 6.4](#)). If subjects terminate prior to Week 56, biomarker samples will be collected at approximately 8, 16 and 24 weeks

after the last dose of SC investigational product was administered (or at Early Termination, as described in [Section 6.4](#)).

If possible, the samples should be obtained following a fasting period of at least 8 hours and at approximately the same time at each study visit to control for variation in the biomarkers related to prandial status and diurnal cycle. The fasting status will be recorded in the eCRF.

Currently the measurement of 12 biomarkers is planned: CCI

This selection of biomarkers could change due to blood volume limitations and/or assay performance issues. Osteoarthritis biomarkers that are different from the ones listed could be added or substituted if considered informative to further understand the osteoarthritis condition.

Instructions regarding sample collection and processing (eg, sample volumes, tube types, storage temperatures) will be provided in the laboratory manual.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

Biomarker samples may be used for further evaluation of biomarkers other than the ones listed that could improve the understanding of the safety and efficacy profile of tanezumab. These data will be used for internal exploratory purposes and will not be included in the clinical report.

The shipment address will be provided to the investigator site prior to initiation of the study.

#### 7.6.2. Urine Biomarkers

For the assessment of the cartilage biomarker CCI urine samples will be collected at Baseline (Day 1; pre-dose), Week 8 (pre-dose), Week 16 (pre-dose) in all subjects.

For subjects that will have activity level monitoring via accelerometry (N ~360), additional biomarker samples will be collected at Week 32 (pre-dose), Week 48 (pre-dose) and at Weeks 56, 64, 80 (or at Early Termination, as described in [Section 6.4](#)). If subjects terminate prior to Week 56, the biomarker samples will be collected at approximately 8, 16 and 24 weeks after the last dose of SC investigational product was administered (or at Early Termination, as described in [Section 6.4](#)).

Urine samples should be collected from the second void of the day or later. If possible, the samples should be obtained following a fasting period of at least 8 hours and at

approximately the same time at each study visit to control for variation in the biomarkers related to prandial status and diurnal cycle. The fasting status will be recorded in the eCRF.

Instructions regarding sample collection and processing (eg, sample volumes, tube types, storage temperatures) will be provided in the laboratory manual.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

Biomarker samples may be used for further evaluation of biomarkers other than the ones listed that could improve the understanding of the safety and efficacy profile of tanezumab. These data will be used for internal exploratory purposes and will not be included in the clinical report.

The shipment address will be provided to the investigator site prior to initiation of the study.

### **7.6.3. Synovial Fluid Biomarkers**

For subjects who had arthrocentesis performed during the study and who provided consent for analysis of synovial fluid samples, additional exploratory analyses of biomarker concentrations in synovial fluid may be undertaken. If deemed appropriate following review of the available safety, synovial fluid and serum concentration (NGF and tanezumab) data, exploratory analyses would be initiated if assay methodology and residual sample volume permit.

## **7.7. Banked Biospecimens**

### **7.7.1. Markers of Drug Response**

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA (deoxyribonucleic acid), RNA (ribonucleic acid), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study.

Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study identification (ID) number. Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not

have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/subject information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/subject information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A 4 mL blood biospecimen **Prep D1 (K<sub>2</sub> EDTA whole blood collection optimized for DNA analysis)** will be collected at the Baseline (Day 1) visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The Banked Biospecimens will be collected from all subjects unless prohibited by local regulations or ethics committee decision. Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

#### 7.7.2. Additional Research

Unless prohibited by local regulations, or ethics committee decision, subjects will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical trial, and related conditions.
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the [Markers of Drug Response](#) Section will be used. Subjects may still participate in the clinical trial if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

## **8. ADVERSE EVENT REPORTING**

### **8.1. Adverse Events**

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a Serious Adverse Event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

### **8.2. Reporting Period**

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through the end of the safety Follow-up period or through and including 112 calendar days after the subject's last administration of the subcutaneous investigational medication if the subject refuses the protocol defined Follow-up period.

Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of investigational product through the subject's last visit.

### **8.3. Definition of an Adverse Event**

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

#### **8.4. Medication Errors**

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the serious adverse event (SAE) form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an adverse event, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE CRF page.

### **8.5. Abnormal Test Findings**

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

### **8.6. Serious Adverse Events**

A Serious Adverse Event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see the section on [Medical Device Complaint Reporting Requirements](#)). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- a life-threatening illness, even if temporary in nature;
- a permanent impairment of a body function or permanent damage to a body structure;
- a condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

Examples: clinically relevant increase in the duration of a surgical procedure, a condition that requires hospitalization or significant prolongation of existing hospitalization;

- any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- fetal distress, fetal death, or any congenital abnormality or birth defects.

#### **8.6.1. Protocol-Specified Serious Adverse Events**

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the Section on [Serious Adverse Event Reporting Requirements](#)).

#### **8.6.2. Potential Cases of Drug-Induced Liver Injury**

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

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- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values  $\geq 3$  times the upper limit of normal (X ULN) concurrent with a total bilirubin value  $\geq 2$  X ULN with no evidence of hemolysis and an alkaline phosphatase value  $\leq 2$  X ULN or not available.
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
  - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT values  $\geq 2$  times the baseline values and  $\geq 3$  X ULN, or  $\geq 8$  X ULN (whichever is smaller).

#### **Concurrent with**

- For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN **or** if the value reaches  $\geq 3$  X ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

#### **8.7. Hospitalization**

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.



### 8.8. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

### 8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (refer to [Section 8.14 Reporting Requirements](#)). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

### 8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

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2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event (SAE) report form and an Exposure During Pregnancy (EDP) Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion.
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

### **8.10.1. Additional Postnatal Development Follow-up**

The Investigator will be asked to assist with collection of assessments of postnatal development as part of a separate protocol. Participation in that protocol is optional and will require that the subject review, agree and sign a separate informed consent document specific to that study, explaining the details of the post-partum follow-up for the subject and the newborn to participate in these assessments of postnatal development.

### **8.11. Occupational Exposure**

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE report form is maintained in the investigator site file.

### **8.12. Withdrawal Due to Adverse Events (See Also [Section 6.4 Subject Withdrawal](#))**

Withdrawal due to AEs should be distinguished from withdrawal due to other causes according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

### **8.13. Eliciting Adverse Event Information**

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

### **8.14. Reporting Requirements**

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

#### **8.14.1. Serious Adverse Event Reporting Requirements**

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

#### **8.14.2. Non-Serious Adverse Event Reporting Requirements**

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

#### **8.14.3. Medical Device Reporting Requirements**

All medical device complaints regardless of whether the medical device complaint is associated with an AE will be collected on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might have led to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

Refer to the Pharmacy Manual for procedures for forwarding medical device complaints not associated with an SAE to Pfizer.

#### **8.14.4. Sponsor's Reporting Requirements to Regulatory Authorities**

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

### **9. DATA ANALYSIS/STATISTICAL METHODS**

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major

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modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

### 9.1. Sample Size Determination

A sample size of approximately 1000 subjects for each of the treatment groups of NSAID, tanezumab 2.5 mg and tanezumab 5 mg will be used in this study. This sample size allows for a high probability of observing subjects with any component of the composite endpoint where the event rate over this study is very small. If the event rate were 0.25%, then there would be a >90% probability of observing at least one subject with an event in any single treatment group.

In addition, the sample size allows for good precision to estimate the incidence rate for each treatment group in order to estimate an upper bound for the true incidence rate. The table below gives the width of the 95% confidence intervals for the individual treatment groups with this sample size.

**Table 10. Estimated Event Incidence Rate Precision**

Observed Rate of Rapidly Progressive Osteoarthritis Type 2	95% Confidence Interval for Individual Treatment Groups (N=1000)
0%	[0, 0.37%]
0.1%	[0.00, 0.56%]
0.2%	[0.02, 0.72%]
0.3%	[0.06, 0.87%]
0.4%	[0.11, 1.02%]
0.5%	[0.16, 1.16%]
1.0%	[0.48, 1.83%]

For the assessment of the incidence of subjects with a total joint replacement, a sample size of approximately 1000 subjects per group would be sufficient to demonstrate a significant difference ( $p \leq 0.05$ ) between any two treatment groups, for a difference of 2% with an observed control group rate for total joint replacement of 2%. Similarly, for the assessment of the incidence of subjects with an adjudication outcome of rapidly progressive osteoarthritis type 2, a sample size of approximately 1000 subjects per group would be sufficient to demonstrate a significant difference ( $p \leq 0.10$ ) between any two treatment groups, for a difference of 1% with an observed control group rate for rapidly progressive osteoarthritis of 0%.

For the efficacy assessments, a sample size of approximately 1000 subjects per group gives 76% power for the treatment comparisons of both tanezumab 5 mg versus NSAID and tanezumab 2.5 mg versus NSAID all three co-primary efficacy endpoints, for assumed treatment differences of -0.73/-0.45 (tanezumab 5 mg/2.5 mg versus NSAID), -0.80/-0.53 and -0.21/-0.11 for WOMAC Pain subscale, WOMAC Physical Function subscale and the Patient's Global Assessment of Osteoarthritis, respectively. The within-group standard deviations were 2.73, 2.58 and 0.92 for WOMAC Pain subscale, WOMAC Physical Function subscale and Patient's Global Assessment of Osteoarthritis, respectively. The correlation of

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the change from Baseline to Week 16 value for WOMAC Pain subscale versus WOMAC Physical Function subscale was 0.93. The correlations between Patient's Global Assessment of Osteoarthritis and WOMAC Pain and Physical Function subscales were approximately 0.68.

*For the Japanese specific efficacy assessments, a sample size of 1000 subjects per group gives 95% power for the treatment comparisons of both tanezumab 5 mg versus NSAID and tanezumab 2.5 mg versus NSAID two co-primary efficacy endpoints, for assumed treatment differences of -0.73/-0.45 (tanezumab 5 mg/2.5 mg versus NSAID) and -0.80/-0.53 for WOMAC Pain subscale and WOMAC Physical Function subscale, respectively. The within-group standard deviations were 2.73 and 2.58 for WOMAC Pain subscale and WOMAC Physical Function subscale of Osteoarthritis, respectively. The correlation of the change from Baseline to Week 16 value for WOMAC Pain subscale versus WOMAC Physical Function subscale was 0.93.*

A sample size of approximately 220 subjects per treatment group is required within each of the three NSAID cohorts (celecoxib, naproxen and diclofenac). This sample size would give an 80% power to detect statistical significance at the 5% significance level, for the comparison of tanezumab 5 mg versus individual NSAID groups in the WOMAC Pain subscale, assuming a treatment difference of -0.73 and a within-group standard deviation of 2.73.

Formal sample size calculation was not performed for the actigraphy data collection, as published actigraphy data in a clinical trial with matched population was not available. However, data from Farr (2008), where the mean minutes of moderate to vigorous physical activity in an OA population is approximately 24 minutes per day, with a standard deviation of 20. Assuming a standard deviation for the change from Baseline of 14 (using a Baseline to post-Baseline correlation of 0.75 to represent strong association in activity over 2 timepoints), then a sample size of 120 subjects per treatment group would give 79 and 91% power for treatment differences of 5 and 6 minutes respectively (approximately 20 and 25% of the Baseline mean shown in this paper).<sup>61</sup>

## **9.2. Primary Analysis**

### **9.2.1. Analysis of Primary Endpoints**

The incidence of subjects with any of the adjudication outcomes of rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture (primary composite endpoint) will be shown by number of subjects treated and subject years of exposure (treatment plus follow-up periods), for individual treatment groups and differences between tanezumab treatment groups and the NSAID treatment group. The risk ratio and risk difference with 95% confidence intervals will be calculated for the comparisons of each tanezumab treatment group versus the NSAID treatment group, as well as significance tests for each treatment comparison. The time to each event will be summarized, and (where there are sufficient numbers of subjects) Kaplan-Meier estimates of the time to event will be produced, together with an analysis of each tanezumab treatment group versus the NSAID treatment group using the log-rank test.

The primary safety and efficacy population will be the ITT population, defined as all randomized subjects who received SC investigational product (either tanezumab or matching placebo). The primary efficacy analysis will use multiple imputation methods for missing data at Week 16. Details of the multiple imputation procedure are given below. All treatment comparisons will use the two-sided 5% significance level.

The co-primary efficacy endpoints will be analyzed using an ANCOVA model, with model terms for Baseline score, Baseline Diary Average Pain, index joint (hip or knee), Kellgren-Lawrence grade, NSAID cohort (diclofenac, celecoxib or naproxen) and treatment group, and study site as a random effect. The assessment of significance for the tanezumab SC versus NSAID treatment contrasts of the primary efficacy parameters will use a step-down testing strategy within each of the co-primary efficacy endpoints. This order of significance testing is defined as first testing tanezumab 5 mg versus NSAID, and if statistically significant ( $p \leq 0.05$ ) to then test tanezumab 2.5 mg versus NSAID. Finally, the tanezumab dose group is declared as superior to NSAID if the corresponding treatment contrast is significant over all three co-primary endpoints (*two co-primary efficacy endpoints in Japan*). This testing procedure will maintain the Type I error to 5% or less within each of the co-primary efficacy endpoints, and to less than 5% for all three co-primary efficacy endpoints (*two co-primary efficacy endpoints in Japan*).

The primary analysis of the co-primary endpoints will use multiple imputation for missing data, to account for uncertainty around the subject response. The basis for imputing missing values will be dependent on the reasons for missing data. For subjects with missing data due to discontinuation prior to Week 16 for lack of efficacy or for an adverse event or death, imputation will be based on sampling from a normal distribution using a mean value equal to the subject's Baseline efficacy value and the standard deviation of the observed efficacy data at Week 16 (over all treatment groups). For subjects with missing data for any other reason, imputation will be based on sampling from a normal distribution using a mean value equal to the subject's last observed efficacy value and standard deviation of the observed efficacy data at Week 16 (over all treatment groups). Imputed values for the Patient's Global Assessment of Osteoarthritis will be rounded to integer values from 1 to 5 (*For Japan, Patient's Global Assessment of Osteoarthritis scores will not be imputed or used in the primary efficacy analysis*). Imputed values for WOMAC Pain and Physical Function subscales will be truncated at 0 and 10. One hundred imputation samples will be used, and the ANCOVA model described above will be used for each imputation dataset. The final results will be calculated using the combined sets of results from each imputation dataset analysis.<sup>4</sup>

Additional analyses will explore the sensitivity of the effect of missing data. The first analysis will use the same main effects ANCOVA model as described above, but with Last Observation Carried Forward (LOCF) for missing data. The second analysis will use the same main effects ANCOVA model as described above, but with Baseline Observation Carried Forward (BOCF) for missing data. The third analysis will use Mixed Model for Repeated Measurements (MMRM) utilizing all observed data up to and including Week 16.

Additional analyses of the primary efficacy endpoints include comparisons of tanezumab 2.5 and 5 mg versus the separate NSAID treatment groups of celecoxib, naproxen and diclofenac. These analyses will not use the testing strategy described above, but assessment of significance will be made across all treatment comparisons and co-primary endpoints individually.

All analyses will show estimates of the treatment group response and treatment group differences of each tanezumab treatment group versus NSAID, with corresponding standard errors of the mean, and 95% confidence intervals (and p-values for treatment differences).

### 9.2.2. Analysis of Secondary Endpoints

The incidence of subjects with any of the adjudication outcomes of rapidly progressive osteoarthritis (type-2), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture will be analyzed as described above for the primary endpoint. In addition the same analysis will be performed for the individual events of all-cause total joint replacements, and adjudicated outcomes of rapidly progressive osteoarthritis (type-1, type-2 and both types 1 and 2 combined), subchondral insufficiency fracture (or SPONK), primary osteonecrosis and pathological fracture.

Secondary efficacy endpoints will examine the change from Baseline to additional timepoints in the WOMAC Pain and Physical Function subscales, and the Patient's Global Assessment of Osteoarthritis, using the multiple imputation for missing data procedure and analysis described above. Other secondary endpoints include the WOMAC Stiffness subscale, WOMAC Average score and WOMAC Pain subscale items (Pain When Walking on a Flat Surface, and Pain When Going Up or Down Stairs), conducted for the change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48 and 56. Analysis of Average Pain in the index joint will be conducted for the change from Baseline to Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40, 48 and 56. The analysis of these endpoints will use the same ANCOVA analysis as described above for the co-primary endpoints, with multiple imputation for missing data.

The OMERACT-OARSI responder index, and subject response endpoints of improvement in the WOMAC Pain  $\geq 30$ , 50, 70 and 90%, WOMAC Physical Function  $\geq 30$ , 50, 70 and 90%, and improvement in the Patient's Global Assessment of Osteoarthritis  $\geq 2$  will be analyzed for change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48 and 56 using logistic regression for binary data, with model terms for Baseline WOMAC Pain subscale score, Baseline WOMAC Physical Function or Baseline Patient's Global Assessment score, Baseline Diary Average Pain, index joint, Kellgren-Lawrence grade, NSAID group and treatment group. The cumulative distribution of percent change to Weeks 16, 24 and 56 in the WOMAC Pain subscale score and WOMAC Physical Function subscale score will be summarized for the response categories of reductions of  $>0\%$ ,  $\geq 10$  to 90% (in steps of 10%) and 100% (no reported pain or difficulties at timepoint of interest). Imputation for missing data will use both LOCF and BOCF, where imputation with BOCF will lead to the subject being assessed as a nonresponder for the response endpoint at a particular timepoint. In addition, in order to closely match the primary imputation analysis, a mixed BOCF/LOCF imputation for response endpoints will be used. In this analysis BOCF imputation (ie, a subject would be a nonresponder) would be used for missing data due to discontinuation for reasons of lack of

efficacy, adverse event or death up to the timepoint of interest, and LOCF imputation would be used for missing data for any other reason.

The change from Baseline in the Patient's Global Assessment of Osteoarthritis to Weeks 2, 4, 8, 16, 24, 32, 40, 48 and 56 will also be analyzed using the Cochran-Mantel-Haenszel test (stratified by the combinations of the three stratification factors). Changes by each level of improvement will be summarized. For this analysis imputation for missing data will use mixed BOCF/LOCF, as well as BOCF and LOCF separately.

The incidence and number of days per week of rescue medication use will be analyzed for Weeks 2, 4, 8, 16, 24, 32, 40, 48 and 56, and the amount of rescue medication use per week will be analyzed for Weeks 2, 4, 8 and 16. The incidence of use of rescue medication will be analyzed using logistic regression for binary data, with model terms for Baseline WOMAC Pain subscale score, Baseline Diary Average Pain, index joint, Kellgren-Lawrence grade, NSAID group and treatment group. The number of days and amount of rescue medication (mg dosage of acetaminophen) will be analyzed using the Negative Binomial model, with model terms of Baseline WOMAC Pain subscale score, Baseline Diary Average Pain, index joint, Kellgren-Lawrence grade, NSAID cohort, and treatment group. Estimated levels of rescue medication use will be shown for each treatment group, and the ratio (with 95% CI) for comparisons versus NSAID will be shown. Imputation for missing rescue medication data will use LOCF only. The incidence and number of days of rescue medication use will be summarized up to Week 64, and the amount of rescue medication taken in a week summarized up to Week 16.

The incidence of and time to withdrawal due to lack of efficacy will also be analyzed for discontinuation up to Week 56 (end of treatment period). The time to discontinuation will be analyzed using the log-rank test, with Kaplan-Meier estimates of the time to discontinuation shown for selected percentiles, dependent on the level of discontinuation. The expectation is that these would be the 1<sup>st</sup>, 2<sup>nd</sup>, 5<sup>th</sup>, 10<sup>th</sup> and 25<sup>th</sup> percentiles. Other percentiles may be shown if the level of discontinuation due to lack of efficacy as calculated using Kaplan-Meier procedure is sufficiently large. The analysis of the incidence of discontinuation due to lack of efficacy will be made using logistic regression for binary data, with model terms for baseline WOMAC Pain subscale score, Baseline Diary Average Pain, index joint, Kellgren-Lawrence grade, NSAID group and treatment group.

A table showing number and percentage of subjects will summarize the response for each dimension (item) of the EQ-5D-5L at Baseline and Weeks 8, 16, 24, 40, 56 and 64. These summary tables will be shown by treatment group. In addition, for each treatment and each time point assessed, descriptive statistics (mean, standard deviation, median, number of subjects) will characterize the five-item health status profile on the EQ-5D-5L in terms of the health utility score and the EQ-VAS.

Summaries of the change from Baseline to Weeks 16, 24, 56 and 64 in the WPAI:OA impairment scores will be shown by treatment group.

All data from TSQM and mPRTI will be summarized by visit. The domains of the TSQM (satisfaction with effectiveness, side effects and convenience and overall satisfaction) and two items of the mPRTI (patient willingness to use drug again; patient preference of drug versus prior treatment) will be analyzed using the Cochran-Mantel-Haenszel test (stratified by the combination of the three stratification factors) at both Weeks 16 and 56. For any analysis using the Cochran-Mantel-Haenszel test, if there are too few subjects in any stratification combination group then an unstratified test will be performed. The HCRU data will be reported as outlined in the Statistical Analysis Plan.

All endpoints up to Week 64 will be summarized (where available), and endpoints up to Week 56 will be analyzed. Any efficacy data collected at the Week 64 visit will be excluded from summary and analyses of efficacy with the following exception: Any efficacy data collected at the Week 64 visit for subjects that have discontinued the study early, and the observations are within 10 weeks after the last dose (8 weeks plus a window of 2 weeks) can be included in the efficacy summaries and analyses for the appropriate efficacy window in which the data falls.

### 9.3. Safety Analysis

Adverse events, concomitant medications, laboratory safety tests, physical and neurological examinations, vital signs, electrocardiogram (ECG), the anti-tanezumab antibody test will be collected for each subject during the study according to the Schedule of Assessments. Standard safety reporting tables will summarize and list the safety data.

Separate adverse event summaries by treatment group for adverse events of decreased sympathetic function will be conducted. More specifically, adverse events with the following preferred terms will be considered to represent adverse events of decreased sympathetic function: Blood pressure orthostatic decreased, bradycardia, dizziness postural, heart rate decreased, orthostatic hypotension, presyncope, sinus bradycardia, syncope, anhidrosis, hypohidrosis, abdominal discomfort, diarrhea, early satiety, fecal incontinence, nausea, vomiting, ejaculation delay, ejaculation disorder, ejaculation failure, hypertonic bladder, micturition urgency, nocturia, urinary frequency, urinary hesitation, urinary incontinence, respiratory distress and respiratory failure. If necessary, this list of preferred terms may be adjusted for updates made to the MEDICAL DICTIONARY FOR DRUG REGULATORY AFFAIRS (MedDRA) dictionary versions used for reporting.

In addition to summaries of adverse events considered to represent adverse events of decreased sympathetic function noted above, adverse events of syncope, bradycardia, orthostatic hypotension, anhidrosis, or hypohidrosis are designated as adverse events of interest that will be reviewed by the unblinded E-DMC (refer to [Section 9.6](#)).

Selected adverse events of interest and common adverse events will be summarized using Risk Differences (with 95% confidence intervals) between each tanezumab group and NSAID. In addition, significance testing will be performed for adverse events of interest between each tanezumab group and NSAID. There will be no multiplicity adjustment for these significance tests.

Incidence of orthostatic hypotension using postural changes in blood pressure, in addition to mean changes in postural blood pressure will be summarized.

The Survey of Autonomic Symptoms (SAS) scores will be summarized by treatment group for the total number of symptoms reported and total impact score. The summary will be shown by visit, and for the change from Baseline.

The Neuropathy Impairment Score (NIS) is the sum of scores over all 37 items from both the Left and Right side. The change from baseline to each post-baseline visit in the NIS (using LOCF for missing data), and to worst (largest) change from Baseline (over all post-Baseline visits) will be summarized, and analyzed using Cochran-Mantel-Haenszel test (stratified by the combinations of three stratification factors). The NIS data, the neurological consultation data and the conclusion from neurological examination data will be reported. The neurological consultation data will be summarized for all subjects, and for subjects with adverse events of abnormal peripheral sensation, which are described in the adverse event section above. The “conclusion from the neurological examination” data will be summarized for each timepoint, and then a summary of the final assessment over all neurological examinations for each subject.

The change from Baseline to Weeks 56 and 80 in the Minimum Joint Space Width (JSW) for subjects with Kellgren-Lawrence grades of 2 or 3 in the index joint will be analyzed for subjects with measurements in the knee and hip separately. The percentage of subjects with narrowing over a certain measurement will be shown, over the range of values from 0 (ie, >0 mm, or any narrowing) to  $\geq 2$  mm, in addition to summary statistics of the mean (with standard error) and median narrowing. Significant progression of osteoarthritis will be defined using the Bland-Altman method,<sup>54</sup> as proposed by OARSI-OMERACT.<sup>55</sup>

Progression will be defined as 1.96 times the within-subject standard deviation of the change in JSW. The incidence of subjects with JSW narrowing greater than or equal to these values will be shown (with Kellgren-Lawrence grades of 2 or 3 in the index joint), and incidence analyzed using logistic regression for binary data, taking into account study site and baseline JSW as covariates. This summary and analysis will be performed separately for subjects with osteoarthritis of the hip and knee. These analyses will use the Week 56 End of Treatment/Early Termination data and then Week 80 End of Study/Early Termination regardless of the study day of assessment and/or where subjects have discontinued early from the study. In the event of missing data, baseline data will not be carried forward for Radiographic data. An additional analysis will be performed for assessments at one year and one and a half years (equivalent to observed data analysis for subjects who reach these timepoints).

### 9.3.1. Anti-Tanezumab Antibodies

The following assessments of anti-tanezumab antibody formation will include:

- For each tanezumab dose arm, a listing of anti-drug antibody test results sorted by subject, dose and nominal time post-dose. The listing of results will also include the actual times post dose.

- For each tanezumab dose arm, the proportion of subjects who develop anti-tanezumab will be summarized.
- Individual subjects with positive anti-tanezumab antibody results will be evaluated for potential impact on the individual's pharmacokinetic, efficacy and safety profile.

#### **9.4. Analysis of Other Endpoints**

##### **9.4.1. Pharmacokinetic Data**

Tanezumab concentrations will be measured to support the development of a SC population PK model that allows for the prediction of the tanezumab concentration over time in individuals. In addition tanezumab concentrations will be measured to inform the immunogenicity profile of tanezumab.

Reporting of PK data will include the following:

- A listing of plasma tanezumab concentrations sorted by subject, dose and nominal time post dose. The listing of concentrations will also include the actual times post dose.
- A descriptive summary of the plasma tanezumab concentrations based on nominal time post dose for each dose.
- A listing of available synovial fluid tanezumab concentrations sorted by subject, dose and nominal time post dose. The listing of concentrations will also include the actual times post dose.
- A descriptive summary of the available synovial fluid tanezumab concentrations based on nominal time post dose for each dose.

##### **9.4.2. Pharmacodynamic (NGF) Data**

Nerve Growth Factor data analyses will be conducted according to the NGF analysis plan.

##### **9.4.3. Biomarker Data**

Biomarker data analysis will be conducted according to the tanezumab biomarker analysis plan.

##### **9.4.4. Physical Activity Level Data**

###### **9.4.4.1. Lower Extremity Activity Scale (LEAS)**

The Lower Extremity Activity Scale score will be a integer value from 1 (bed bound) to 18 (competitive athlete). The number and percentage of subjects whose activity score is improved (increased), worsened (decreased) or have no change will be shown by treatment group for Weeks 4, 8, 16, 24, 56 and 80 (using LOCF for any missing data). The change from baseline to each post-baseline visit (using LOCF for missing data), and for the worst

change from Baseline (over all post-Baseline visits) will be summarized, and analyzed using Cochran-Mantel-Haenszel test.

#### **9.4.4.2. Actigraphy**

Monitoring of physical activity level via actigraphy will be conducted in approximately 360 subjects.

A valid day of monitoring will be defined as 10 or more wear hours in a 24-hour period as verified from accelerometer output. During Screening, a complete monitoring period will be defined as containing at least 1 valid weekend day of data and a minimum of 4 valid days of monitoring. During activity level monitoring between Week 14 and the Week 16 visit and between Week 54 and the Week 56 visit, a complete monitoring period will be defined as containing at least 2 valid weekend days of data and a minimum of 8 valid days of monitoring.

An average daily activity count will be calculated for each subject. These data will then be sorted into three intensity thresholds: light, moderate and vigorous physical activity levels. The intensity count thresholds for each of these activity levels are described in the statistical analysis plan. The data will be further summarized as total daily time (minutes) for each intensity level. From these data the following parameters will be calculated:

1. Average daily physical activity counts.
2. Average daily minutes of physical activity.
3. Average daily minutes of moderate to vigorous physical activity (MVPA).
4. Average daily minutes of bouted MVPA. A “bout” is defined as 10 or more consecutive minutes above the moderate physical activity level threshold, with allowance for interruptions of 1 or 2 minutes below the threshold.
5. Average daily step count.

The change from Baseline to Week 16 and 56 will be calculated for these parameters. Summaries and analyses of these endpoints will use observed data for change from Baseline to Weeks 16 and 56, and imputation using last observation carried forward for Week 56.

These parameters will be analyzed using the Negative Binomial model, with model terms of Baseline activity score, index joint, Kellgren-Lawrence grade, NSAID cohort, and treatment group. Estimated levels of each activity parameter will be shown for each treatment group, and the ratio (with 95% CI) for comparisons versus NSAID will be shown.

#### **9.5. External Adjudication Committee**

A blinded Adjudication Committee consisting of external experts in orthopedic surgery, rheumatology, orthopedic pathology, or radiology with expertise in subjects with end stage osteoarthritis and osteonecrosis will be convened. The Adjudication Committee will have

written operating procedures and a Charter, including a specific description of the scope of their responsibilities. In general, the Adjudication Committee will be asked to review all possible or probable joint-related safety events identified by the Central Reader (refer to [Section 7.4.5](#)), total joint replacement, as well as investigator reported adverse events of osteonecrosis, rapidly progressive osteoarthritis, subchondral insufficiency fracture (spontaneous osteonecrosis of the knee [SPONK]) or pathologic fracture. Adverse events related to joint safety that the investigator or sponsor considers medically important may also be reviewed by the Adjudication Committee. These will include, but will not be limited to events identified for adjudication by the Central Reader (refer to [Section 7.3.10](#)).

Prior to the Adjudication Committee's review of a given event, the Committee will be provided with blinded, available source documentation of progress reports from the investigator, orthopedic consult reports, operative reports, radiology reports, pathology reports, X-ray images, MRI images, and pathology specimens for review. Copies of all relevant clinical information including the items listed above should be provided to Pfizer or its designee for review by the external Adjudication Committee. Copies of the information should include the study number, site number and subject number, but it should not include the subject's name or initials.

The E-DMC will be provided with a blinded summary of the Adjudication Committee's review of events after each review meeting.

#### **9.6. Data Monitoring Committee**

An independent, E-DMC has been instituted for the tanezumab clinical program. This committee will be composed of at least one rheumatologist, neurologist, statistician, and epidemiologist. The E-DMC will review unblinded safety data including (but not limited to) adverse events and serious adverse events on a regular basis throughout the trial. Adverse events of syncope, bradycardia, orthostatic hypotension, anhidrosis or hypohidrosis along with other adverse events that are possibly related to the sympathetic nervous system will be monitored by the E-DMC during review of unblinded safety data. The E-DMC will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities.

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the Charter. If the blinded Adjudication Committee identifies adjudicated events of rapidly progressive osteoarthritis type 2, subchondral insufficiency fracture (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis or pathological fracture, occurring at a rate that could trigger the protocol-based stopping criteria, an urgent, ad hoc assessment of the events will be made by the E-DMC.

Any recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

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Pfizer Standard Operating Procedures regarding periodic safety reviews by the study team and the Tanezumab Risk Management Committee will be followed. This committee will be composed of members inside and outside the immediate study team who will review blinded safety data from individual studies as well as data pooled across the studies on an ongoing basis. A safety review plan will be in place governing the frequency and extent of safety review.

### **9.6.1. Protocol-Level Rules for Dosing Suspension/Safety Assessment**

#### **9.6.1.1. Serious Adverse Events**

Tanezumab safety will be reviewed at two levels; blinded data reviews by Pfizer and unblinded reviews by the E-DMC. The E-DMC will review unblinded safety data including adverse events and serious adverse events on a regular basis throughout the course of these studies. Pfizer performs blinded review of all serious adverse event data (including those serious adverse events specified below) and a cumulative review on a monthly basis. If blinded review notes a pre-specified serious adverse event occurring at a rate that could trigger the protocol-based dosing suspension rule (ie, at least 3 or more cases of a given pre-specified serious adverse event), an urgent, ad hoc assessment by the E-DMC will be conducted. The E-DMC will determine whether a protocol-based dosing suspension rule should be triggered. At the individual protocol-level, if a given pre-specified serious adverse event is reported in 3 more subjects in any individual tanezumab treatment group than for control group subjects, the protocol-based rule for dosing suspension will be triggered.

The pre-specified serious adverse events are:

- Sudden cardiac death or cardiac death.
- Acute renal failure.
- Anaphylactic shock or severe anaphylactic reaction.
- Neuropathic joint or neuropathic arthropathy (ie, Charcot joint).
- Peripheral neuropathy confirmed with objective findings such as treatment-emergent abnormalities on neurologic examination, nerve conduction abnormalities or biopsy findings consistent with peripheral neuropathy.
- One of the events related to sympathetic dysfunction (orthostatic hypotension, bradycardia, syncope, anhidrosis, or hypohidrosis).

If a protocol-based rule for dosing suspension is triggered, it will result in suspension of further dosing of subjects in the study until a decision is reached regarding whether it is safe to resume dosing in some or all treatment groups or whether the study should be terminated completely. This decision will be made by the Sponsor in consultation with the tanezumab E-DMC.

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If the protocol-based stopping rule is triggered, the E-DMC will consider the implications of this action on a program-level basis and formulate a recommendation whether it is safe to continue dosing (for some or all treatment groups) in other ongoing tanezumab clinical studies. Decisions regarding stopping treatment in other ongoing tanezumab clinical studies will be made by the Sponsor in consultation with the E-DMC.

Factors that may be considered in making this decision in relation to serious adverse events or adjudicated clinically significant adverse events include:

- Consideration of relationship of investigational product to the adverse event.
- Consideration of whether similar adverse events are occurring in other tanezumab studies with similar subject populations.
- Dosage of tanezumab (2.5 mg or 5 mg) and distribution of adverse events across tanezumab dose arms.
- Possible differences in the baseline demographics between treatment groups.
- Use of concomitant medications.
- Possible differences in baseline medical history and/or co-morbidities.
- Duration of therapy (0-6 months, 6-12 months).

#### **9.6.1.2. Events Consistent with Hy's Law**

If two events are reported which are consistent with Hy's Law in tanezumab-treated subjects, irrespective of dose across all ongoing osteoarthritis and chronic low back pain studies, dosing will be temporarily suspended in all studies until the relationship to study drug is established for the given events which were consistent with Hy's Law. If two events consistent with Hy's Law are considered to be related to treatment with tanezumab or the cause cannot be determined, all dosing in the tanezumab osteoarthritis and chronic low back pain program may be stopped. The E-DMC will determine whether the dosing suspension should be triggered. Subsequently the E-DMC will formulate a recommendation whether all studies should be permanently terminated. Decisions regarding permanently stopping treatment and terminating studies will be made by the Sponsor in consultation with the DMC.

#### **9.6.2. Joint Safety Events**

If the blinded Adjudication Committee identifies adjudicated events of rapidly progressive osteoarthritis type 2, subchondral insufficiency fractures (or spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture occurring at a combined rate that could trigger the protocol-based stopping criteria, an urgent, ad hoc assessment of the events will be made by the Data Monitoring Committee.

The protocol (or treatment group) stopping rule has three components; the difference in the number of subjects with an adjudicated joint safety event, the exposure-adjusted risk

difference (RD) and the exposure adjusted risk ratio (RR) between each tanezumab treatment group and the active comparator group. The exposure-adjusted RD will be calculated as the difference in the ratios of the number of subjects with an adjudicated joint safety event divided by exposure (patient-years) between each tanezumab group and the comparator group. The exposure-adjusted RR will be similarly calculated using the ratio of exposure adjusted event rates (number of subjects with an adjudicated joint safety event divided by exposure) for each tanezumab group relative to the comparator group. The exposure will be calculated as the combined treatment and follow-up periods.

If the RD is [REDACTED] and the RR is [REDACTED] and the difference in the number of subjects with adjudicated events joint safety events [REDACTED] for any tanezumab treatment group versus the comparator treatment group, the protocol-based stopping rule will be triggered. If the protocol-based stopping rule is triggered, the E-DMC will formulate a recommendation whether it is safe to continue dosing in some or all treatment groups or whether the study should be terminated completely. This decision will be made by Pfizer in consultation with the E-DMC.

## 10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## **11. DATA HANDLING AND RECORD KEEPING**

### **11.1. Case Report Forms/Electronic Data Record**

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

### **11.2. Record Retention**

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to the International Conference on Harmonisation (ICH) guidelines, local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## **12. ETHICS**

### **12.1. Institutional Review Board (IRB)/Ethics Committee (EC)**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the Investigator File. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

### **12.2. Ethical Conduct of the Study**

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

### **12.3. Subject Information and Consent**

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data, in any reports, publications, or in any other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, address, birth date and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

#### **12.4. Subject Recruitment**

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

#### **12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP**

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

### **13. DEFINITION OF END OF TRIAL**

#### **13.1. End of Trial in a Member State**

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by

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a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

### **13.2. End of Trial in all other Participating Countries**

End of trial in all other participating countries is defined as database lock.

## **14. SPONSOR DISCONTINUATION CRITERIA**

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of tanezumab at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 1 week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

## **15. PUBLICATION OF STUDY RESULTS**

### **15.1. Communication of Results by Pfizer**

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or [www.pfizer.com](http://www.pfizer.com), and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Pfizer posts clinical trial US Basic Results on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

*Primary completion* date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

[EudraCT](http://www.eudra-ct.eu)

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year

of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

[www.pfizer.com](http://www.pfizer.com)

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on [www.pfizer.com](http://www.pfizer.com) for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

## **15.2. Publications by Investigators**

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the Study is part of a multi center study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the (Clinical Study Agreement) CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

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If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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## Abbreviations

This is a list of abbreviations that may or may not be used in the protocol.	
Abbreviation	Term
Ab	antibody
ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AEMPS	Agency on Medicinal Products and Medical Devices
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASA	American Society of Anesthesiologists
AST	aspartate aminotransferase
BID	twice a day
BMI	body mass index
BOCF	baseline observation carried forward
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
CCI	
CCI	
CCI	
CPK	creatine phosphokinase
CRF	case report form
CR	controlled release
CRA	Clinical Research Associate
CCI	
CSA	clinical study agreement
CT	computed tomography
CTA	clinical trial application
CTS	carpal tunnel syndrome
CCI	
CCI	
CYP	cytochrome enzyme system
DAAP	United States Food and Drug Administration Division of Analgesia, Anesthetic, and Addiction Products
DAI	Dosage and Administration Instructions
DNA	deoxyribonucleic acid
DXA	dual energy x-ray absorptiometry
EC	Ethics Committee
ECG	electrocardiogram
E-DMC	External Data Monitoring Committee
EDTA	edetic acid (ethylenediaminetetraacetic acid)

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EIU	exposure in-utero
EQ-5D-5L	EuroQol 5 Dimension
ER	extended release
ESR	erythrocyte sedimentation rate
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HBsAg	hepatitis B surface antigen
CCI	
HCV	hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HR	heart rate
CCI	
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICRP	International Commission on Radiation Protection
CCI	
IND	Investigational New Drug application
INR	International Normalized Ratio
IgG	immunoglobulin G
IgG2	immunoglobulin G Type 2
IPAP	Initial Pain Assessment Period
IRB	institutional review board
IL	interleukin
IL-1 $\beta$	Interleukin-1 beta
CCI	
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IV	intravenous
JSW	joint space width
LDH	lactate dehydrogenase
LEAS	Lower Extremity Activity Scale
LFT	liver function test
LOCF	Last Observation Carried Forward
LSLV	last subject last visit
LSMean	least squared mean
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MHRA	Medicines and Healthcare products Regulatory Agency
CCI	

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MMRM	mixed model for repeated measures
mPRTI	Patient Reported Treatment Impact assessment-modified
MMR	measles, mumps and rubella
MR	magnetic resonance
MRI	magnetic resonance imaging
mSv	millisievert
MVPA	moderate to vigorous physical activity
N/A	not applicable
NCI	National Cancer Institute
NGF	nerve growth factor
NGFI	nerve growth factor inhibitor
NIS	Neuropathy Impairment Score
NNH	number needed to harm
NNT	number needed to treat
NRS	numeric rating scale
NSAID	non-steroidal anti-inflammatory drug
NSC	Neuropathy Symptom Change
NYHA	New York Heart Association
OA	osteoarthritis
CC	
OMERACT-OARSI	Outcome Measures in Rheumatology – Osteoarthritis Research Society Initiative
OTC	over-the-counter
PCD	primary completion date
PD	pharmacodynamic
PEI	Paul Ehrlich Institute
PGA	Patient Global Assessment
PHQ-9	Patient Health Questionnaire
CCI	
PK	pharmacokinetic
PO	oral administration (per os)
PT	prothrombin time
PTH	parathyroid hormone
QD	once daily
QT	in electrocardiography, the time corresponding to the beginning of depolarization to repolarization of the ventricles
QTc	in electrocardiography, the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate
QTcB	QT corrected for heart rate using Bazett's formula
QTcF	QT corrected for heart rate using Fridericia's formula
RD	risk difference
RNA	ribonucleic acid
RPOA	rapidly-progressive osteoarthritis

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## **Appendix 1. American American College of Rheumatology (ACR) Classification Criteria for Osteoarthritis**

### **1986 Osteoarthritis Knee Criteria**<sup>54</sup>

Clinical and radiographic criteria for classification of idiopathic osteoarthritis of the knee.

Meets criteria 1, 2 and 3:

1. Knee pain.
2. Presence of at least 1 of the following 3:
  - Age greater than 50 years.
  - Morning stiffness less than 30 minutes in duration.
  - Crepitus.
3. Presence of osteophytes on X-ray.

### **Osteoarthritis Hip Criteria**<sup>56</sup>

Combined clinical (history, physical examination, laboratory) and radiographic criteria for osteoarthritis of the hip, traditional format.

1. Hip pain.
2. AND at least 2 of the 3 following features:
  - Erythrocyte sedimentation rate (ESR) less than 20 mm/hour.
  - Radiographic femoral or acetabular osteophytes.
  - Radiographic joint space narrowing (superior, axial, and/or medial).

Because the presence of osteophytes on X-ray is a protocol requirement (defined by a Kellgren-Lawrence X-ray Grade of  $\geq 2$  in inclusion criteria #3), protocol defined requirement for diagnosis of osteoarthritis of the hip will be the presence of hip pain, presence of osteophytes on X-ray and either an ESR < 20 mm/hour OR joint space narrowing on X-ray.

ESR testing may be conducted at the local laboratory.

## **Appendix 2. American Society of Anesthesiologists (ASA) Physical Status Classification**

### **ASA Physical Status Classification**

The ASA physical status classification system is used for assessing the fitness of patients before surgery. In 1963 the American Society of Anesthesiologists (ASA) adopted the five-category physical status classification system;<sup>57</sup> a sixth category was later added (<http://www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System>).

1. A normal healthy patient.
2. A patient with mild systemic disease.
3. A patient with severe systemic disease.
4. A patient with severe systemic disease that is a constant threat to life.
5. A moribund patient who is not expected to survive without the operation.
6. A declared brain-dead patients whose organs are being removed for donor purposes.

### Appendix 3. Half-Lives of Prohibited Prior and Concomitant Medications

#### Half-Lives of NSAIDs and Other Analgesics

Use of analgesics (including marijuana) except acetaminophen / paracetamol is prohibited through Week 64 of the study beginning 48 hours prior to the start of the IPAP (the seven days prior to Randomization/Baseline (Day 1) or at the period of time prior to the start of the IPAP that is at least 5 times the half-life of the particular analgesic used, whichever is greater. Note that a stable regimen of aspirin taken for cardiac prophylaxis at a dose of  $\leq 325$  mg/day is permitted throughout the study.

These lists are not all-inclusive. The Physician's Desk Reference provides half-life information.

<b>HALF-LIVES OF NSAIDs AND OTHER ANALGESICS</b>		
<b>Analgesic</b>	<b>Half-life (hours)</b>	<b>Minimum Washout Period</b>
Aspirin >325 mg/day	0.25	2 days
Azapropazone	15.0	4 days
Bromfenac	1.3-3.1	2 days
Capsaicin (cream, ointments, patches)	2.0	2 days
Carprofen	12.0	3 days
Celecoxib	11.0	3 days
Codeine	3.5	2 days
Diclofenac gels	1.9	2 days
Diclofenac	1.1	2 days
Diclofenac/misoprostol	2.4-9.0	2 days
Diflunisal	13.0	3 days
Dipyrrone	2.0-5.0	2 days
Etodolac	6.0	2 days
Fenbufen	11.0	3 days
Fentanyl	Contact study clinician	
Fenoprofen	2.5	2 days
Flufenamic acid	1.4	2 days
Flurbiprofen	3.8	2 days
Hydrocodone	4.5	2 days
Hydromorphone	3.0	2 days
Ibuprofen	2.1	2 days
Indomethacin	4.6	2 days
Ketoprofen	1.8	2 days
Ketorolac	4.0-9.0	2 days
Lidocaine patch or EMLA (lidocaine/prilocaine)	2.0	2 days
Meclofenamate	2.0-4.0	2 days

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<b>HALF-LIVES OF NSAIDs AND OTHER ANALGESICS</b>		
Mefenamic acid	2.0	2 days
Meloxicam	16.0 to 20.0	5 days
Meperidine	3.7	2 days
Mexiletine	6.0-17.0	4 days
Morphine	2.0	2 days
Nabumetone	26.0	6 days
Naproxen	14.0	3 days
Oxaprofen	40.0-50.0	11 days
Oxaprozin	58.0	13 days
Oxycodone	3.2	2 days
Oxycodone CR	8.0	2 days
Oxymorphone	7.3-9.4	2 days
Phenylbutazone	68.0	15 days
Piroxicam	57.0	12 days
Pirprofen	3.8	2 days
Propoxyphene	12.0	3 days
Salicylates	2.0-15.0	4 days
Sulindac	14	3 days
Suprofen	2.5	2 days
Tapentadol	4	2 days
Tenoxicam	60.0	13 days
Tiaprofenic acid	3.0	2 days
Tolmetin	1.0	2 days
Tramadol	5.9	2 days

**Corticosteroids** The following use of oral or intramuscular corticosteroids is prohibited through Week 64 of the study and: 1) within 30 days prior to the Initial Pain Assessment Period (the seven days prior to Randomization/Baseline) or, 2) at the period of time prior to the start of the Initial Pain Assessment Period that is at least 5 times the half-life of the particular corticosteroid used, whichever is greater or, 3) the anticipated need to start such during the study. Intra-articular injection of corticosteroids within 12 weeks to the index joint or to any other joint within 30 days prior to the Initial Pain Assessment Period is PROHIBITED. Topical, inhaled and intranasal corticosteroids are PERMITTED.

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<b>Corticosteroids</b>	
<b>Generic</b>	<b>Brand</b>
betamethasone	Celestone, Soluspan
Cortisone	
dexamethasone	Decadron, Dexacort, Turbinaire
fludrocortisone	Florinet
hydrocortisone	A-hydroCort, Cortef, Hydrocortone, Solu-Cortef
methylprednisolone	Medrol, Solu-Medrol
Prednisolone	Orapred, Prelone
Prednisone	Cortan, Deltasone, Medicorten

### **Hyaluronic Acid**

Intra-articular hyaluronic acid injection to the index knee is prohibited within 30 days (or within 18 weeks for long-acting formulations such as Synvisc) of the Initial Pain Assessment Period and throughout the study.

### **Biologicals**

Use of biologicals is prohibited within 3 months of the Initial Pain Assessment Period and during the study.

The following lists are provided for your reference but may not be all-inclusive. Refer to the Physician's Desk Reference for exclusion determination of a particular agent.

<b>TNF<math>\alpha</math> Inhibitors</b>	
<b>Generic</b>	<b>Brand</b>
Adalimumab	Humira
Etanercept	Enbrel
Infliximab	Remicade

Use of live attenuated vaccines (with the exception of Flumist<sup>®</sup> Influenza Virus Vaccine Live, Intranasal or other inhaled live attenuated influenza vaccines and Pneumovax) is prohibited within 3 months of Initial Pain Assessment Period and during the study.

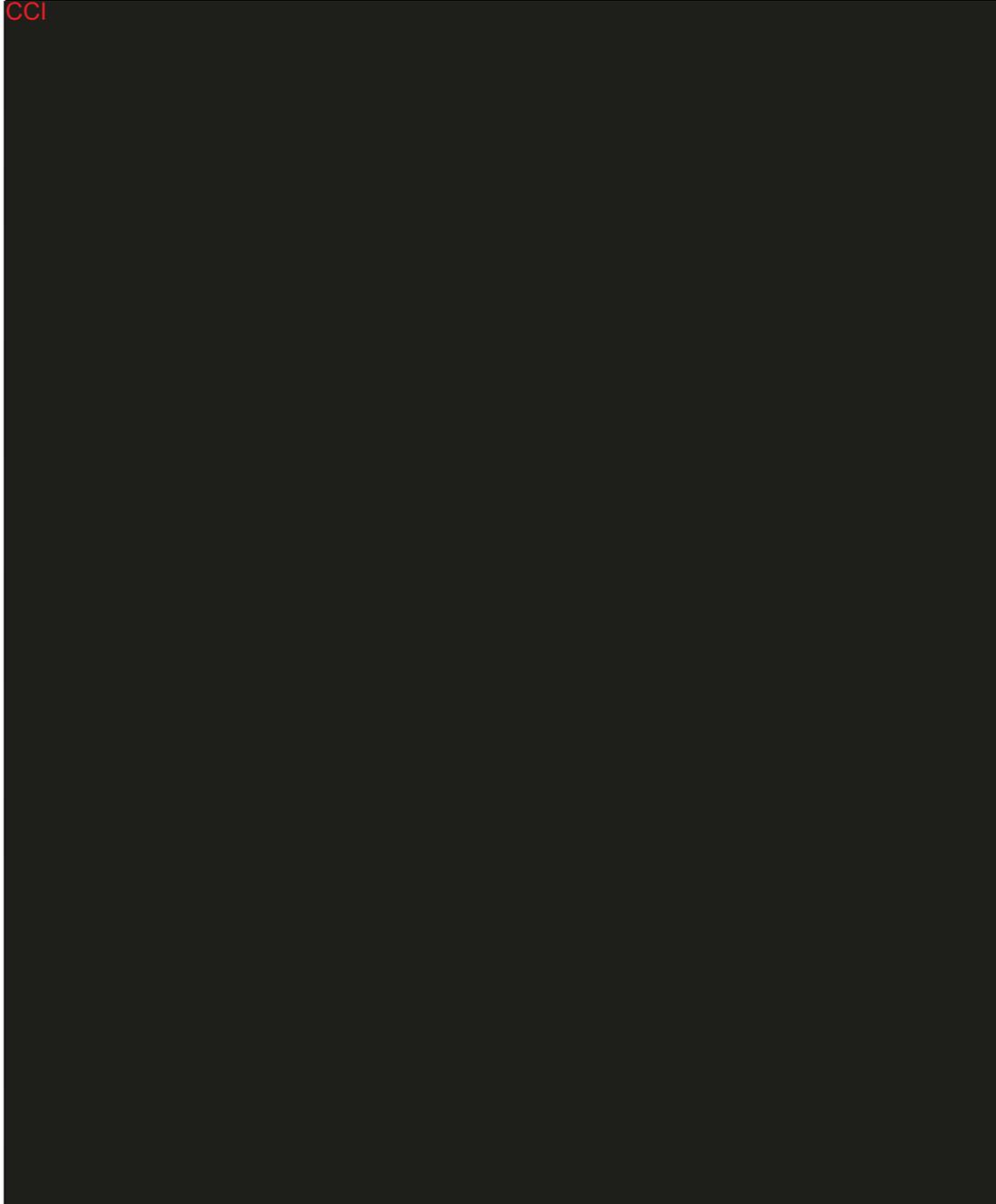
The following lists are provided for your reference but may not be all-inclusive. Refer to the Physician's Desk Reference for exclusion determination of a particular agent.

<b>Live Attenuated Vaccines</b>	
<b>Generic</b>	<b>Brand</b>
BCG (for tuberculosis)	Not available in the US
Herpes zoster vaccine	Zostavax
Influenza, intranasal	FluMist
Measles	Attenuvax
Measles, Mumps, and Rubella (MMR)	MMR
Mumps	Mumpsvox
Oral poliovirus vaccine, oral	OPV (no longer available in the US)
Rotavirus, oral	RotaTeq
Rubella	Meruvax II
Smallpox	Dryvax (Not commercially available in the US)
Typhoid, oral	Vivotif Berna
Varicella zoster	Varivax
Yellow fever	YF-VAX

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## Appendix 4. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

### WOMAC Osteoarthritis Index NRS3.1



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WOMAC NRS 3.1 – English for USA – V5

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## WOMAC Osteoarthritis Index NRS3.1

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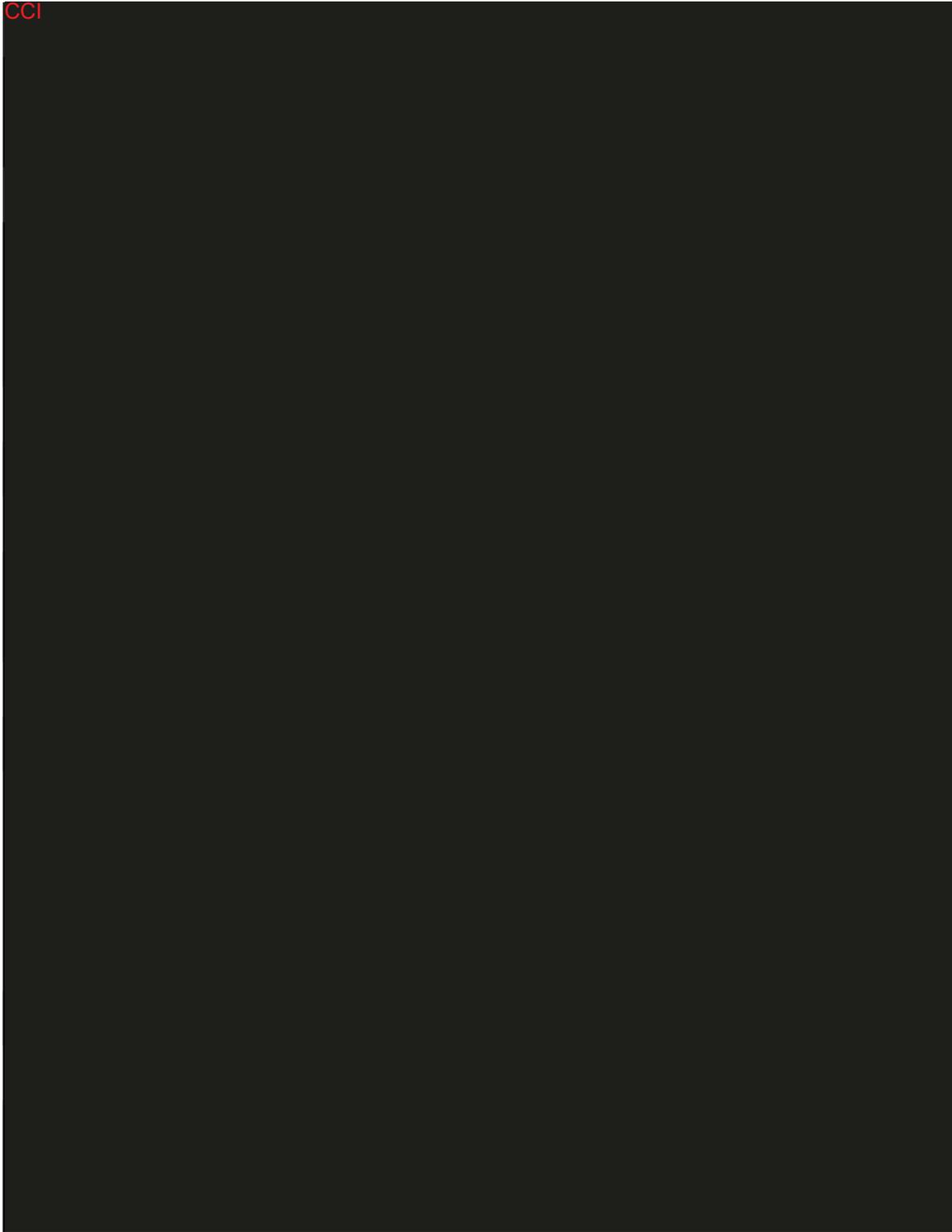


WOMAC NRS 3.1 – English for USA – V5

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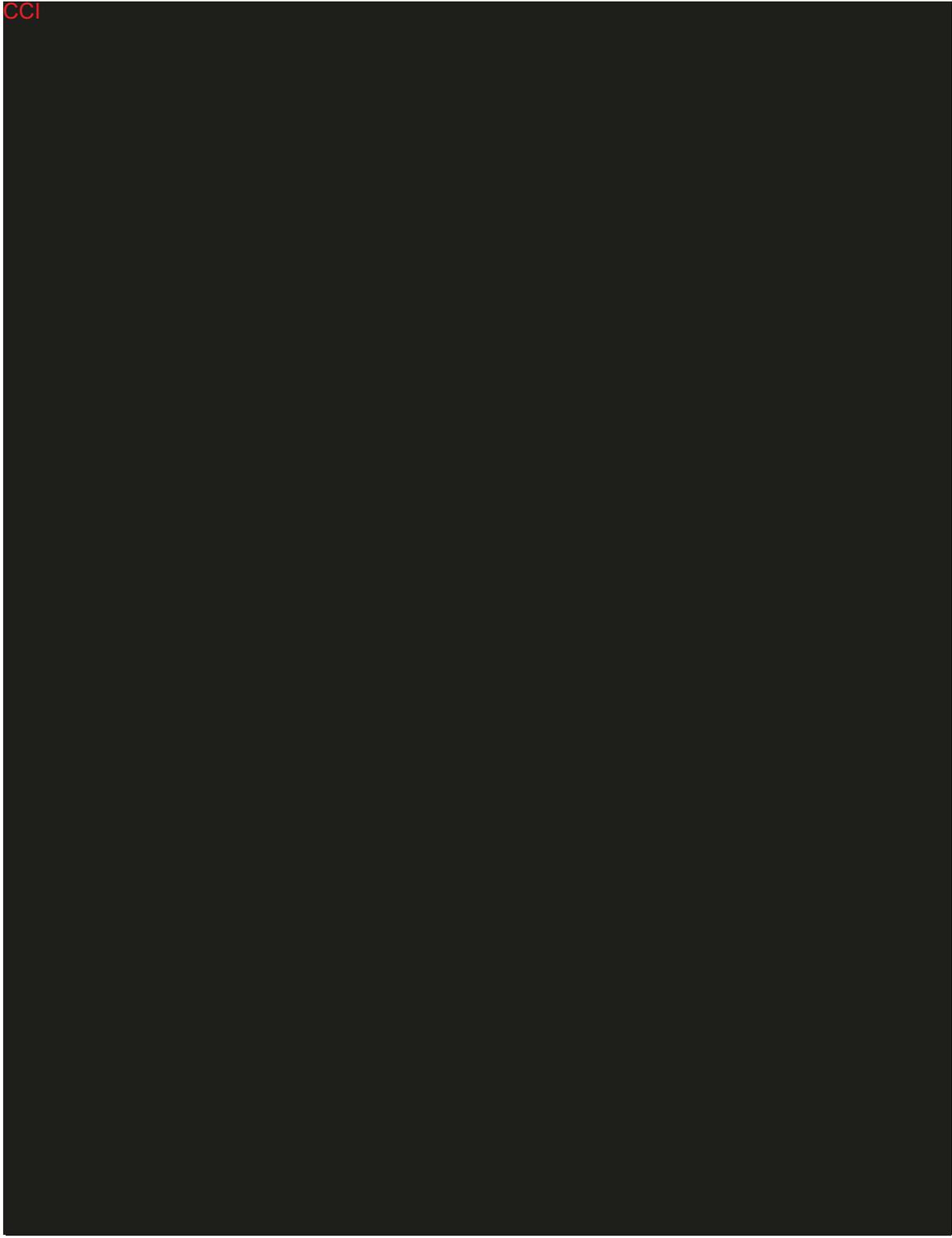


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## **Appendix 5. Patient's Global Assessment of Osteoarthritis**

### **Patient's Global Assessment of Osteoarthritis – Knee**

Subjects will answer the following question when the knee is selected as index joint:

Considering all the ways your osteoarthritis in your knee affects you, how are you doing today?

Subjects will rate their condition using the following scale:

<b>Grade</b>	<b>Description</b>
1 – Very Good	Asymptomatic and no limitation of normal activities
2 – Good	Mild symptoms and no limitation of normal activities
3 – Fair	Moderate symptoms and limitation of some normal activities
4 – Poor	Severe symptoms and inability to carry out most normal activities
5 – Very Poor	Very severe symptoms which are intolerable and inability to carry out all normal activities

### **Patient's Global Assessment of Osteoarthritis – Hip**

Subjects will answer the following question when the hip is selected as index joint:

Considering all the ways your osteoarthritis in your hip affects you, how are you doing today?

Subjects will rate their condition using the following scale:

<b>Grade</b>	<b>Description</b>
1 – Very Good	Asymptomatic and no limitation of normal activities
2 – Good	Mild symptoms and no limitation of normal activities
3 – Fair	Moderate symptoms and limitation of some normal activities
4 – Poor	Severe symptoms and inability to carry out most normal activities
5 – Very Poor	Very severe symptoms which are intolerable and inability to carry out all normal activities



5. During the past seven days, how much did your osteoarthritis of the knee or hip affect your productivity while you were working?

*Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If osteoarthritis of the knee or hip affected your work only a little, choose a low number. Choose a high number if osteoarthritis of the knee or hip affected your work a great deal.*

Consider only how much osteoarthritis of the knee or hip affected productivity while you were working.

Osteoarthritis of the knee or hip had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Osteoarthritis of the knee or hip completely prevented me from working
--	---	---	---	---	---	---	---	---	---	---	----	--

CIRCLE A NUMBER

6. During the past seven days, how much did your osteoarthritis of the knee or hip affect your ability to do your regular daily activities, other than work at a job?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If osteoarthritis of the knee or hip affected your activities only a little, choose a low number. Choose a high number if osteoarthritis of the knee or hip affected your activities a great deal.*

Consider only how much osteoarthritis of the knee or hip affected your ability to do your regular daily activities, other than work at a job.

Osteoarthritis of the knee or hip had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Osteoarthritis of the knee or hip completely prevented me from doing my daily activities
--	---	---	---	---	---	---	---	---	---	---	----	--

CIRCLE A NUMBER

WPAI:OA V2.0 (US English)

## Appendix 7. EuroQol 5 Dimension (EQ-5D-5L)

---

By placing a check mark in one box in each group below, please indicate which statements best describe your own health state today.

### Mobility

- I have no problems walking
- I have slight problems walking
- I have moderate problems walking
- I have severe problems walking
- I am unable to walk

### Self-Care

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

### Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

### Pain/Discomfort

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

### Anxiety/Depression

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

SAMPLE

Continued to next page

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We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

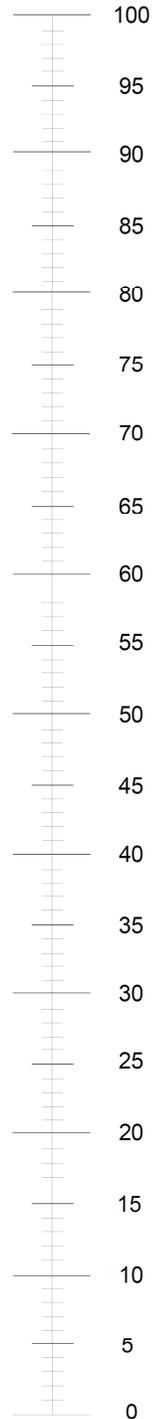
100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

The best health  
you can imagine



SAMPLE

Health State:

The worst health  
you can imagine

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**Appendix 9. Patient Health Questionnaire (PHQ-9)**

Administration of the PHQ-9 is not mandatory but may be used by the investigator to assess the severity of depression. The severity score is the sum of questions 1-9 only. A score of 15 or higher on questions 1 through 9 indicates severe depression. If used the PHQ-9 should be stored in the subject file. The results of this instrument will not be entered into a database, nor will it be analyzed.

**PATIENT HEALTH QUESTIONNAIRE (PHQ-9):**

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
1. Little interest or pleasure in doing things	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Feeling down, depressed, or hopeless	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Trouble falling or staying asleep, or sleeping too much	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Feeling tired or having little energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Poor appetite or overeating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Trouble concentrating on things, such as reading the newspaper or watching television	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Thoughts that you would be better off dead or of hurting yourself in some way	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Total Score: \_\_\_\_

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

<b>Not difficult at all</b>	<b>Somewhat difficult</b>	<b>Very difficult</b>	<b>Extremely difficult</b>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

PHQ-9 is adapted from PRIME MD TODAY, developed by Drs Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr Kroenke at [kkroenke@regenstrief.org](mailto:kkroenke@regenstrief.org). Use of the PHQ-9 may only be made in accordance with the Terms of Use available of <http://www.pfizer.com>. Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.

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## Appendix 10. Osteoporosis Risk Factors<sup>58</sup>

<b>Osteoporosis Risk Factors</b>		
<b>Lifestyle Factors</b>		
Low calcium intake	Vitamin D insufficiency	Excess vitamin A
High caffeine intake	High salt intake	Aluminum (antacid use)
Alcohol (≥ 3 drinks / day)	Inadequate physical activity	Immobilization
Smoking (active or passive)	Falling	Thinness
<b>Genetic Factors</b>		
Cystic fibrosis	Homocystinuria	Osteogenesis imperfect
Ehlers-Danlos	Hypophosphatasia	Parental history of hip fracture
Gaucher's disease	Idiopathic hypercalciuria	Porphyria
Glycogen storage disease	Marfan syndrome	Riley-Day syndrome
Hemochromatosis	Menkes steely hair syndrome	
<b>Hypogonadal States</b>		
Androgen insensitivity	Hyperprolactinemia	Turner's & Klinefelter's syndromes
Anorexia nervosa bulimia	Panhypopituitarism	
Athletic amenorhea	Premature ovarian failure	
<b>Endocrine Disorders</b>		
Adrenal insufficiency	Diabetes mellitus	Thyrotoxicosis
Cushing's syndrome	Hyperparathyroidism	
<b>Gastrointestinal Disorders</b>		
Celiac disease	Inflammatory bowel disease	Primary biliary cirrhosis
Gastric bypass	Malabsorption	
GI surgery	Pancreatic disease	
<b>Hematologic Disorders</b>		
Hemophilia	Multiple myeloma	Systemic mastocytosis
Leukemia and lymphomas	Sickle cell disease	Thalassemia
<b>Rheumatic and Autoimmune Diseases</b>		
Ankylosing spondylitis	Lupus	Rheumatoid arthritis
<b>Miscellaneous Conditions and Diseases</b>		
Alcoholism	Emphysema	Muscular dystrophy
Amyloidosis	End stage renal disease	Parenteral nutrition
Chronic metabolic acidosis	Epilepsy	Post-transplant bone disease
Congestive heart failure	Idiopathic scoliosis	Prior fracture as an adult
Depression	Multiple sclerosis	Sarcoidosis
<b>Medications</b>		
Anticoagulants (heparin)	Cancer chemotherapeutic drugs	Gonadotrophin releasing hormone agonists
Anticonvulsants	Cyclosporine A and tacrolimus	Lithium
Aromatase inhibitors	Depo-medroxyprogesterone	
Barbiturates	Glucocorticoids (≥5 mg/day of prednisone or equivalent for ≥3 months)	

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## Appendix 11. American College of Radiology Safety Screening Form and Magnetic Resonance Hazard Checklist<sup>59</sup>

### SAFETY SCREENING FORM FOR MAGNETIC RESONANCE (MR) PROCEDURES

Date \_\_\_\_\_  
Name (first middle last) \_\_\_\_\_  
Female [ ] Male [ ] Age \_\_\_\_\_ Date of Birth \_\_\_\_\_  
Height \_\_\_\_\_ Weight \_\_\_\_\_  
Why are you having this examination (medical problem)?  
\_\_\_\_\_

**YES NO**  
Have you ever had an MRI examination before and had a problem?  
\_\_\_\_\_

If yes, please describe \_\_\_\_\_  
Have you ever had a surgical operation or procedure of any kind?  
\_\_\_\_\_

If yes, list all prior surgeries and approximate dates:  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Have you ever been injured by a metal object or foreign body (e.g., bullet, BB, shrapnel)?  
\_\_\_\_\_

If yes, please describe \_\_\_\_\_  
\_\_\_\_\_

Have you ever had an injury from a metal object in your eye (metal slivers, metal shavings, other metal object)?  
\_\_\_\_\_

If yes, did you seek medical attention? \_\_\_\_\_  
If yes, describe what was found \_\_\_\_\_

Do you have a history of kidney disease, asthma, or other allergic respiratory disease?  
\_\_\_\_\_

Do you have any drug allergies?  
\_\_\_\_\_

If yes, please list drugs \_\_\_\_\_

Have you ever received a contrast agent or X-ray dye used for MRI, CT, or other X-ray or study?  
\_\_\_\_\_

Have you ever had an X-ray dye or magnetic resonance imaging (MRI) contrast agent allergic reaction?  
\_\_\_\_\_

If yes, please describe \_\_\_\_\_

Are you pregnant or suspect you may be pregnant?  
\_\_\_\_\_

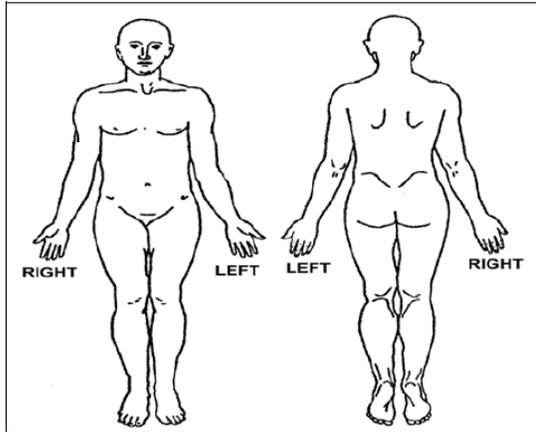
Are you breast feeding?  
\_\_\_\_\_

Date of last menstrual period \_\_\_\_\_ Post-menopausal? \_\_\_\_\_

### MR Hazard Checklist

Please mark on the drawing indicating the location of any metal inside your body or site of surgical operation.

The following items may be harmful to you during your MR scan or may interfere with the MR examination. You must provide a "yes" or "no" for every item. Please indicate if you have or have had any of the following:



**YES NO**

\_\_\_\_\_ Any type of electronic, mechanical, or magnetic implant  
Type \_\_\_\_\_

\_\_\_\_\_ Cardiac pacemaker  
\_\_\_\_\_ Aneurysm clip  
\_\_\_\_\_ Implantable cardiac defibrillator  
\_\_\_\_\_ Neurostimulator  
\_\_\_\_\_ Biostimulator

Type \_\_\_\_\_

\_\_\_\_\_ Any type of internal electrodes or wires  
\_\_\_\_\_ Cochlear implant  
\_\_\_\_\_ Hearing aid  
\_\_\_\_\_ Implanted drug pump (e.g., insulin, baclofen, chemotherapy, pain medicine)  
\_\_\_\_\_ Halo vest  
\_\_\_\_\_ Spinal fixation device  
\_\_\_\_\_ Spinal fusion procedure  
\_\_\_\_\_ Any type of coil, filter, or stent

Type \_\_\_\_\_

\_\_\_\_\_ Any type of metal object (e.g., shrapnel, bullet, BB)  
\_\_\_\_\_ Artificial heart valve  
\_\_\_\_\_ Any type of ear implant  
\_\_\_\_\_ Penile implant  
\_\_\_\_\_ Artificial eye  
\_\_\_\_\_ Eyelid spring

\_\_\_ Any type of implant held in place by a magnet

Type \_\_\_\_\_

\_\_\_ Any type of surgical clip or staple

\_\_\_ Any IV access port (e.g., Broviac, Port-a-Cath, Hickman,  
PICC line)

\_\_\_ Medication patch (e.g., nitroglycerine, nicotine)

\_\_\_ Shunt

\_\_\_ Artificial limb or joint

What and where \_\_\_\_\_

\_\_\_ Tissue expander (e.g., breast)

\_\_\_ Removable dentures, false teeth, or partial plate

\_\_\_ Diaphragm, IUD, pessary

Type \_\_\_\_\_

\_\_\_ Surgical mesh

Location \_\_\_\_\_

\_\_\_ Body piercing

Location \_\_\_\_\_

\_\_\_ Wig, hair implants

\_\_\_ Tattoos or tattooed eyeliner

\_\_\_ Radiation seeds (e.g., cancer treatment)

\_\_\_ Any implanted items (e.g., pins, rods, screws, nails, plates, wires)

\_\_\_ Any hair accessories (e.g., bobby pins, barrettes, clips)

\_\_\_ Jewelry

\_\_\_ Any other type of implanted item

Type \_\_\_\_\_

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## Appendix 12. Lower Extremity Activity Scale<sup>48</sup>

**Lower Extremity Activity Scale\***

Please read through each description given below, pick the ONE description that best describes your regular daily activity and put a check in that box (Check only one box).

- 1. I am confined to bed all day. (1)
- 2. I am confined to bed most of the day except for minimal transfer activities (going to the bathroom, etc.) (2)
- 3. I am either in bed or sitting in a chair most of the day. (3)
- 4. I sit most of the day, except for minimal transfer activities, no walking or standing. (4)
- 5. I sit most of the day, but I stand occasionally and walk a minimal amount in my house. (I may rarely leave the house for an appointment and may require the use of a wheelchair or scooter for transportation.) (5)
- 6. I walk around my house to a moderate degree but I don't leave the house on a regular basis. I may leave the house occasionally for an appointment. (6)
- 7. I walk around my house and go outside at will, walking one or two blocks at a time. (7)
- 8. I walk around my house, go outside at will and walk several blocks at a time without any assistance (weather permitting). (8)
- 9. I am up and about at will in my house and can go out and walk as much as I would like with no restrictions (weather permitting). (9)
- 10. I am up and about at will in my house and outside. I also work outside the house in a:
  - minimally (10)
  - moderately (11)
  - extremely active job (12)(Please check the best description of your work level.)
- 11. I am up and about at will in my house and outside. I also participate in relaxed physical activity such as jogging, dancing, cycling, swimming:
  - occasionally (2-3 times per month) (13)
  - 2-3 times per week (14)
  - daily (15)(Please check the best description of how often you participate in this activity.)
- 12. I am up and about at will in my house and outside. I also participate in vigorous physical activity such as competitive level sports
  - occasionally (2-3 times per month) (16)
  - 2-3 times per week (17)
  - daily (18)(Please check the best description of how often you participate in this activity.)

\* actual score obtained is specified in parentheses at end of whichever statement is chosen

Fig. 1

The lower-extremity activity scale (LEAS).

## Appendix 13. Treatment Satisfaction Questionnaire Medicine v.II

### **TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION - VERSION II TSQM:**

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication over the last two to three weeks, or since you last used it. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

- (1) Extremely Dissatisfied
- (2) Very Dissatisfied
- (3) Dissatisfied
- (4) Somewhat Satisfied
- (5) Satisfied
- (6) Very Satisfied
- (7) Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

- (1) Extremely Dissatisfied
- (2) Very Dissatisfied
- (3) Dissatisfied
- (4) Somewhat Satisfied
- (5) Satisfied
- (6) Very Satisfied
- (7) Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

- (1) Yes
- (0) No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

- (1) Extremely Dissatisfied
- (2) Very Dissatisfied
- (3) Somewhat Dissatisfied
- (4) Slightly Dissatisfied
- (5) Not at all Dissatisfied

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5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

- (1) Extremely Dissatisfied
- (2) Very Dissatisfied
- (3) Somewhat Dissatisfied
- (4) Slightly Dissatisfied
- (5) Not at all Dissatisfied

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

- (1) Extremely Dissatisfied
- (2) Very Dissatisfied
- (3) Somewhat Dissatisfied
- (4) Slightly Dissatisfied
- (5) Not at all Dissatisfied

7. How satisfied or dissatisfied are you with how easy the medication is to use?

- (1) Extremely Dissatisfied
- (2) Very Dissatisfied
- (3) Dissatisfied
- (4) Somewhat Satisfied
- (5) Satisfied
- (6) Very Satisfied
- (7) Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

- (1) Extremely Dissatisfied
- (2) Very Dissatisfied
- (3) Dissatisfied
- (4) Somewhat Satisfied
- (5) Satisfied
- (6) Very Satisfied
- (7) Extremely Satisfied

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9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

- (1) Extremely Dissatisfied
- (2) Very Dissatisfied
- (3) Dissatisfied
- (4) Somewhat Satisfied
- (5) Satisfied
- (6) Very Satisfied
- (7) Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

- (1) Extremely Dissatisfied
- (2) Very Dissatisfied
- (3) Dissatisfied
- (4) Somewhat Satisfied
- (5) Satisfied
- (6) Very Satisfied
- (7) Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

- (1) Extremely Dissatisfied
- (2) Very Dissatisfied
- (3) Dissatisfied
- (4) Somewhat Satisfied
- (5) Satisfied
- (6) Very Satisfied
- (7) Extremely Satisfied

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Appendix 15. Survey of Autonomic Symptoms (SAS)<sup>60</sup>

**Table 1** Survey of Autonomic Symptoms\*

Symptom/health problem	Q1a. Have you had any of the following health symptoms during the past 6 months? (1 = Yes; 0 = No)	Q1b. If you answered yes in Q1a, how much would you say the symptom bothers you? (1 = Not at all; 2 = A little; 3 = Some; 4 = A moderate amount; 5 = A lot)
1. Do you have lightheadedness?	1 0	1 2 3 4 5
2. Do you have a dry mouth or dry eyes?	1 0	1 2 3 4 5
3. Are your feet pale or blue?	1 0	1 2 3 4 5
4. Are your feet colder than the rest of your body?	1 0	1 2 3 4 5
5. Is sweating in your feet decreased compared to the rest of your body?	1 0	1 2 3 4 5
6. Is sweating in your feet decreased or absent (for example, after exercise or during hot weather)?	1 0	1 2 3 4 5
7. Is sweating in your hands increased compared to the rest of your body?	1 0	1 2 3 4 5
8. Do you have nausea, vomiting, or bloating after eating a small meal?	1 0	1 2 3 4 5
9. Do you have persistent diarrhea (more than 3 loose bowel movements per day)?	1 0	1 2 3 4 5
10. Do you have persistent constipation (less than 1 bowel movement every other day)?	1 0	1 2 3 4 5
11. Do you have leaking of urine?	1 0	1 2 3 4 5
12. Do you have difficulty obtaining an erection (men)?	1 0	1 2 3 4 5

\* Number of symptoms reported: \_\_\_\_ (sum of column A, 0-12 for men and 0-11 for women); total symptom impact score: \_\_\_\_ (sum of column B, 0-60 for men and 0-55 for women).

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